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Section of Comparative Medicine

President—Professor A. HADDOW, M.D., D.Sc., Ph.D.

[*October* 18, 1950]

Advances in the Study of Chemical Carcinogenesis

PRESIDENT'S ADDRESS

By Professor A. HADDOW, M.D., D.Sc., Ph.D.

IT will be easy for you to understand how it is that I, more perhaps than most, should wish to acknowledge a special debt to comparative pathology and comparative medicine, inasmuch as the field of cancer investigation, more than almost any other, has been dependent—indeed utterly dependent—upon the comparative method. Although we have by far the greater part still to learn, our accumulated knowledge is already vast, and we recall with gratitude—to mention only a very few examples—the early work upon tumour transplantation, such names as that of Leo Loeb, the unravelling of cancer genetics in the mouse, Peyton Rous' discovery of the avian tumour virus which bears his name and still provides us with a great opportunity as well as an enigma now forty years old, Bashford's great work on the natural history of cancer in the animal kingdom, and the much more recent demonstration of the Bittner virus as a factor in the causation of mammary cancer in mice—all discoveries of the first order in the comparative field. Little do they know of cancer who only cancer know: the subject is in fact almost coterminous with cell biology itself and equally dependent for its advance upon advances in the basic sciences as a whole. Here indeed lies one of its greatest attractions—not only do we draw upon the basic sciences in applying them to our special problem, but we may also hope, partly by labour but more often by good fortune, to repay the debt. This is strikingly so too in the case of comparative pathology, which has at once catalysed and fostered the growth of our knowledge of cancer and at the same time been itself abundantly enriched.

Chemical carcinogenesis is the subject in which one is most engrossed; it is a research in which the chase becomes ever more enthralling as the months and years go by. In this field comparative pathology again provides us with our first lesson—namely, that carcinogenic potency is no absolute property of a given chemical substance but is dependent for its expression upon a great range of factors amongst which specific, genetic, and organ and tissue differences rank as the most important. Many years of the most patient research into the metabolic history and fate of individual carcinogenic substances, when these are introduced into the tissues of different animal species, are only now beginning to yield a glimpse of the reasons why such substances may readily provoke the appearance of tumours in one species or in one set of circumstances, and not at all in another.

When we speak of recent advances in the field of chemical carcinogenesis we forget that the bulk of work in the subject has been carried out only in the past three decades, in the whole of which period the pace of advance has been considerable. Thus it is only a matter of thirty-five years since the first experimental chemical production of cancer by the Japanese; only twenty-one years since the first production of cancer by a pure chemical individual in the shape of 1:2:5:6-dibenzanthracene, by my predecessor Sir Ernest Kennaway; and only fifteen years since we first developed the view that the carcinogenic hydrocarbons may operate by specific damage to the growth mechanism of the normal cell, which then reacts by the adaptive development of a new mechanism—the nature of which still eludes us—and the emergence of what is for all practical purposes a new cell race. In the meantime we have collected a vast quantity of information relating to hundreds of chemical carcinogens—the carcinogenic hydrocarbons, concerning which so much was contributed by Kennaway, Cook, Hieger, Hewett and others; the carcinogenic azo dyestuffs, to the study of which we again owe so much to the Japanese; and a large number of aromatic amines, including β-naphthylamine, 2-acetamidofluorene, and most recently a whole series of aminostilbenes.

In all these cases we have acquired a great deal of knowledge as to the relationship between chemical structure and biological action—both within a series and sometimes linking one series and another. But in no case—a striking fact—do we know the place in the cell at which they act—whether the cell surface, the cytoplasm, the nuclear membrane, the nucleus itself—or the nature of the receptors with which they combine. Only very recently have we obtained our first hints as to (1) the more precise nature of the mechanism of action, and (2) the site in the cell at which it takes place. These hints—and of course they are for the moment no more—have arisen entirely in the past three years and very largely from the discovery, in this short interval, of the carcinogenic potency of the nitrogen mustards.

Most here are no doubt familiar with the history of the nitrogen mustards as potential chemical warfare agents, and with their limited therapeutic application especially in Hodgkin's disease. It appeared not unreasonable to expect to improve the therapeutic efficiency of these substances by chemical modification, and in the past three years some 250 variants have been synthesized, by Kon, Ross and others at the Royal Cancer Hospital, and have been tested biologically to this end. Although the chemical possibilities are certainly far from exhausted, therapeutic usefulness has proved difficult to increase. On the other hand, the wider biological investigation of these substances has led to considerable advances of a more fundamental kind, which are, in fact, beyond anything we had in mind, or could, perhaps, have expected. The first approach was to decide in which aromatic amines, if any, *bis*chloroethyl or similar groups could be inserted and still confer the cytotoxic activity characteristic of the aliphatic nitrogen mustards. From extensive clinical trials carried out with a few of these substances (and particularly with the *bis*chloroethyl derivative of β-naphthylamine), it appears that the therapeutic effects are very largely confined to those tumour types already known to be responsive to the aliphatic mustards. From cytological evidence it appears too that the action of these substances, as in the aliphatic series, is very largely direct, as shown by the production of chromosome breaks, of bridges at anaphase, and of defects in chromosome spiralization; the last effect is specially important in view of what I shall have to say of the mechanism of action. The chromosome fragments appear to be ejected into the cytoplasm, where they agglomerate as "micronuclei," this process being repeated in successive divisions in each of which the cell accumulates further nuclear damage until it is no longer viable: the essential damage—of which the aberrations during mitosis are the sequel—is, however, believed to occur in the so-called resting stage between divisions.

All the biological phenomena included in their clinical and cytological effects are such as to justify the description of these compounds as radiomimetic, and the same analogy is apparent in the damage to cell division which they can produce in hæmopoiesis and spermatogenesis, as also in a remarkable and apparently permanent greying or bleaching or hair which appears over the site of intracutaneous or subcutaneous injection in coloured mice; the last effect is quite indistinguishable from that induced by X-radiation or the subcutaneous injection of a radioelement such as plutonium. These observations have led to the development of the concept of radioequivalence as between ionizing radiations and such chemical agents, not only as regards their effects *in vivo* but also *in vitro*, where the reactions brought about by both types of agent with deoxyribonucleic acid show a quantitative correspondence greater than would appear to be due to chance alone. These facts, as also the observation of Elson that the growth-inhibitory effects of these aromatic mustards, like those of the carcinogenic hydrocarbons and aminostilbenes, appeared to be increased by a sufficiently low concentration of protein in the diet, made it desirable to determine whether the aromatic nitrogen mustards might, equally with ionizing radiations, be capable of producing tumours, as a further expression of radiomimetic action. Tests of selected compounds were therefore carried out in the rat, mouse, and hamster, and with abundantly positive result, tumours having been produced in all these species at the site of application. A feature of the tumours induced by subcutaneous injection has been the frequent coincident appearance of sarcoma and carcinoma, and it is also possible to induce intestinal carcinoma, by administration orally. As a class, all these tumours have proved of the greatest interest cytologically, on account of the high proportion with nuclear abnormalities (of the same general types as those produced by the mustards acutely). Indeed it would seem in these cases as though the tumour cells bear the imprint of the causal carcinogen, and it is of additional interest that in certain tumours the visible chromosomal abnormalities may be perpetuated through many transplanted generations, although they tend to die out, no doubt through some selective process, after a shorter or longer time.

These facts and findings have certain implications, and allow certain inferences. In the first place, while cytological abnormalities have frequently been observed in individual tumours induced by other carcinogens, such as the cyclic hydrocarbons, their interpretation has been difficult, and their significance doubtful, on account of their inconstancy and the fact that they might, in other cases, be entirely absent. In the present instance we have been compelled to study these nuclear changes more closely, even if only on account of their relative frequency, and admitting that they are unlikely to be causally connected with tumour induction and propagation, and no doubt only associated. One may conjecture whether the frequency of such abnormalities in the mustard-induced tumours may be a reflection of the high chemical reactivity of these substances, in contrast say with the carcinogenic hydrocarbons. Again, in the nitrogen mustard series there might appear to be a greater prospect than with the hydrocarbons, on account of this high reactivity and their relatively simple molecular structure, of deciphering the mode of action. In a long series we were impressed by the apparent dependence of biological activity on a certain degree of chemical reactivity, and on the presence in the molecule of a minimum of two reactive side-chains: this bifunctional or polyfunctional requirement had previously been commented upon by others, for the sulphur mustards as well as their nitrogen analogues. In an endeavour to interpret this situation, Goldacre, Loveless and Ross had suggested, from general considerations of the adsorption of drugs to proteins, from the aspect of chemical cytology, and from kinetic studies of the reactions of "two-armed" compounds, that such bi- or polyfunctional agents might operate through a process of chemical cross-linking between the constituent linear macro-molecules of the chromosome structure itself. We now know that this

explanation is unduly exclusive, and we cannot for instance dismiss a two-armed combination along the length of such molecular fibres, rather than between them, or other processes involving regular polymerization (such as has been suggested by Rose), or indeed a more random molecular arborization. The main importance of the hypothesis lies in its suggestion of direct chemical combination of the carcinogenic molecule with genetic material, and in this sense it has proved highly fertile in development. In this connexion a great deal of help has come from the field of textile cross-linking, as for instance from Speakman's suggestion of the di-epoxides, many of which do in fact duplicate the biological action of the nitrogen mustards and are the first of a whole series of chemical types all yielding the same carbonium ion. The cross-linking potentiality is not, however, sufficient, and reaction must occur first of all under mild conditions, and, secondly (according to Ross), with acid groups preferentially, and not for example with sulphydryl or amino groups alone. As indicated, however, there are undoubtedly other possibilities, such as reaction at two sites on a single fibre to give rings of varying stability, polymerization, arborization, and even swamping of the biological sites or receptors by one-armed compounds.

Until recently, our picture of the carcinogenic process envisaged damage of the normal growth mechanism as the primary effect. At present (at least so far as the mustards are concerned), we now picture damage to the chromosome by direct combination with genetic material, followed maybe by the generation of a new and self-duplicating chemical and genetic rearrangement. A primary effect on the nucleus would not of course be surprising, although we are so far quite ignorant as to whether such combination, through cross-linking or other means. is between say polypeptide chains or via the nucleoprotein. All this has greatly influenced our recent thinking upon the subject of carcinogenesis, has to some extent clarified it, and is already leading to fresh development. The process I have hypothetically described is not dissimilar from that of globulin and immune body production from a fibre, surface or template secreting by replication, or liberating a specific protein, and in this connexion it is not without interest that the cell types most sensitive to the action of the nitrogen mustards (the lymphocyte, the plasma-cell, and reticulo-endothelial cells more generally) include those which may be, according to one view, responsible for immune body production. More recently, certain of the compounds under discussion have been shown (by Ford and by Revell) to have a varying degree of preferential action at certain specific chromosome regions, especially the so-called heterochromatic regions known to have characteristic chemical and genetic properties, the latter associated not so much with Mendelian inheritance as with the quantitative inheritance of growth-rate and differentiation features and their mutation. It is perhaps a sign of the times, and some indication of progress, that while the mouse was selected some thirty years ago as the most suitable test object for carcinogenicity studies, on account of its availability, susceptibility, short life-span and ease of maintenance, we are now searching for both animal and plant material with cytological features of the greatest advantage. Much help is also being gathered from studies of the relationship between carcinogenesis and mutation. Here again there is great need for a more detailed knowledge of chromosome structure, such as can only become available in the decades ahead. Meantime, however, as has been the case with other cytogenetic problems—and cancer is one such—we hope to acquire further information from the concomitant changes induced in the giant chromosome of the *Drosophila* salivary gland. It is clear that an immense amount still remains to be accomplished, but from what I have said there would appear to be—and for the first time—some prospect (if only a prospect) of correlating the chemical properties of a given carcinogen with the chemical properties of specific chromosome regions, with the resultant cytological effects, and with the genetic consequences to the cell which thus ensue.

Section of General Practice

President—G. F. Abercrombie, V.R.D., M.A., M.D., K.H.P.

[*January* 17, 1951]

DISCUSSION ON INFLUENZA

Dr. E. P. Scott: The correct diagnosis in the early stages of any disease is of paramount importance. Frequently we all see cases of influenza in which in these early stages we would welcome further opinions, but are diffident because relatives of the patient might consider—and quite rightly so—that this attitude is an alarmist one. It is undesirable and indeed impracticable to hospitalize the mild type of case, although we all know that this presently may develop into something far more serious. Incidentally a case of influenza is *non persona grata* in any institution for the obvious reason of infection.

In General Practice, in probably the greater majority of medical cases with fever, influenza is the tentative diagnosis. I have attempted, therefore, briefly to discuss the pitfalls of such as seen in General Practice, and would emphasize this.

May I start, first of all, by asking ourselves, "What is influenza?" The origin of the word influenza is fascinating: It comes from the Italian and was reputed to be a disease which was caused by an ethereal fluid flowing from the stars, hence the name.

Beaumont has admirably defined it in his "Medicine" as "An acute disease of doubtful ætiology, characterized by fever, prostration, a great liability to pulmonary complications, and to epidemic incidence". I cannot help feeling that the word "doubtful" is a masterly description!

There have been many epidemics of disease in history, and it has been mooted, I believe, that some of these have been influenza, e.g. the Black Death might well have been a cyanotic 'flu.

I again reiterate that nearly every medical case, with temperature, is diagnosed firstly as influenza, and this ranges from the condition known as "common cold" to an acute pyrexial state, to say nothing of all the other conditions whose incipient symptoms simulate that disease.

I remember well several epidemics, more especially in the early 'thirties, and the peculiar selection of fatality in cases that I saw in the same family, where, obviously, the infection was the same, one healthy young person being very ill, and a much older one, less so. Of many outstanding cases in my memory, I recall tragedy in two families; in both instances young people died: in one, a girl of 20 succumbed to the disease in a few days, while her grandmother, a chronic bronchitic of 72, came through with flying colours. In the other, an apparently healthy young woman, and mother of three fine children, there was a rapidly fatal issue with acute fulminating cyanotic influenza, while her husband, who was many years older and not, in my opinion, a very good life, recovered from the disease some four days after the death of his spouse.

To the laity this distressing complaint is generally associated with a condition of fever, prostration, and extreme boredom at incarceration, and is reckoned to be of about three to eight days' duration or more. This of course is, economically, a very serious state of affairs, and I would be interested to know how many man-hours are wasted every year by such incapacity.

To us, however, in General Practice, influenza is quite a different problem. We are the people who see this condition in the first three or four days, and I would imagine that no consultant physician ever does so. It is in these first four days that the importance of diagnosis arises.

Influenza, to us, also ranges from the so-called feverish cold to severe illness and fever, and these symptoms are frequently present in the much graver issues which may follow or be simulated. May I give a list of these—which have occurred in my own and, I presume, in all our experiences? Most common, incipient acute respiratory disease; infective hepatitis; tuberculosis; cerebrospinal fever; of the specific fever group, measles, the paratyphoids and the colon-typhoid group; pyelitis, and many others; and last, but not least, I have seen a case of carcinoma of the lung which had been diagnosed in its initial stage as influenza; but you will note that I am not discussing any complications which may occur in the course of the disease *per se*, such as myocarditis, endocarditis, otitis, &c., because, by this time, the diagnosis is generally established, and I feel that this aspect should be reviewed by Sir Horace Evans rather than by myself.

I consider that by far the most sinister aspect of influenza is its occurrence in a patient with some chronic or intercurrent disease or lesion. We all appreciate the seriousness of an infection superimposed on a chronic bronchiectatic, or a long-standing cardiac lesion, to say nothing of fractures and recent abdominal section.

I would like to add here that, not being an obstetrician, I never see young children, so my experience of this disease in them is perfunctory.

We must consider also other illnesses which have been diagnosed in the past *erroneously* as influenza.

I saw recently an interesting case. It was that of a young man with Parkinsonism. I saw him originally in an influenza epidemic some three or four years ago. The symptoms were quite atypical and indeed I well remember that I was puzzled at the time, but I diagnosed him as influenza and treated him as such. He did not appear to be gravely ill at the time. I think there was no question of doubt that I was mistaken, and that he had had a mild encephalitis. It is in the epidemics that mistakes are so liable to occur. I think that all of us, during these times, have erred; but I have formulated in my own mind what to look for when a patient's temperature does not abate after the third or fourth day, for, as I have stated, that is about the time that the subject may start showing signs of other disease. It is when this happens that doubts still assail me as to whether I am right. It is all very well if a patient is being skilfully and professionally nursed, but when one is seeing frequent cases of the same type, it is surely understandable that some other disease occurring during the epidemic may be missed.

In 1941, when I was in the Army, there was an epidemic of influenza among the troops and young medical officers had sick parades of as many as 50 or more in a morning, all of them with varying degrees of pyrexia. In one camp a very young medical officer, and therefore with little experience, failed to diagnose a case of cerebrospinal meningitis, with disastrous and fatal results. But I learnt something of great value when I met a very highly qualified, experienced medical officer and skilful physician. He agreed with me about the difficulty, but said one thing which I must say I have not forgotten, and which has stood me in good stead ever since. He said this: "If ever you have a case of influenza, and the patient, after three or four days, does not begin to clear on the usual remedies, or if vomiting has intervened, always be suspicious of some more serious condition." Since then I have found his wise advice right in every instance, and this is particularly so in my experience in those cases of influenza which are not respiratory. In this connexion I am referring to infective hepatitis. This is a condition of which I have seen a goodly number of cases in the last twenty years. Practically *every one* of them has been diagnosed as 'flu

until the nausea and vomiting ushered in jaundice. What a difficult situation one is placed in when this happens, as it did recently with a patient of mine, a man of large business interests, whom I told on the second day, a Friday, that I thought he would probably be back to his office on the Monday. On the Sunday night he was sick, and I saved my reputation—and added to my prestige, I hope—by asking his wife on the telephone, to look at her husband's eyes. I waited for a moment, and she came back and said that she could see nothing wrong with them and that they were still the same clear blue!—to which I expressed a hope that they would be of the same colour the next day. The following morning he had jaundice!

I do not intend to discuss any of the different types of influenza which are so well known—by this I mean the respiratory, abdominal, &c.—nor their causation, as to whether they are bacterial or virus, but these, of course, are of great importance inasmuch as treatment depends largely on these factors.

As we all know, the usual treatment depends on the type of the disease, and I will very briefly discuss this:

(1) *Prophylactic and preventive.*—By this I mean the general measures of avoidance of infection, and exposure to cold; also the numerous drugs, antihistamines, injection therapies, &c., largely advertised in the medical press. I will only mention two of these: the prophylactic influenzal vaccines, and the anti-virus vaccines. Of the former I have little to say, and of the latter I have so far not had sufficient experience in numbers to discuss it, and await to hear with interest Dr. Andrewes' views on this subject.

(2) *Curative.*—Before the days of antibiotics I suppose every case was treated by salicylates and addenda in one form or another, and I still largely employ these. Sulphonamides and penicillin have, of course, made a great difference in disease, but I am sure that the latter is too widely used in the initial stages, possibly in many cases due to the request of the patient himself, and one is very occasionally tempted to concur. Of course, we all know the futility of giving penicillin in cases in which the infection is resistant to it, but again, if one ventures to suggest that sputum, &c., be tested for sensitivity, it is felt by the patient, at this early stage, that unnecessary fuss is being made. One is therefore sometimes diffident about such procedure. I cannot help feeling that the injudicious use of penicillin in these cases neither prevents nor aborts the disease, but it does one thing which is far more sinister—it liberates to the community at large other organisms which by now may have become penicillin resistant. I have found it of little use in the so-called virus infections or those of the abdominal type, and indeed I now rarely employ it for such. Sulphonamides I use largely and find them highly active, but they frequently depress many patients and this effect is often resented.

In the recent epidemic of influenza at least two of my cases have had pyrexia of a severe grade, 103·5° to 104·5° F., and neither penicillin nor sulphonamides gave any response whatsoever.

In all minor cases of doubtful origin I generally prescribe the usual salicylate compounds in heavy doses, with good results. Some time ago, before it was procurable here, I was given by an American friend of mine a small quantity of aureomycin, then practically unknown in this country, which I jealously guarded against the time I might employ it, possibly in cases of influenza. In the first instance the result was dramatic—an attractive young lady of 22 years, with a temperature of 102·5° F., late on a Friday afternoon, after administration of aureomycin could not be prevented, either by parental or medical authority, from dancing at a night club on the Saturday evening, apparently perfectly well!

The next cases were a couple—and again the lady reacted similarly. Naturally I told the husband, who developed the condition a little later, that he need have no worry and that he would be able to shoot his pheasants in two days' time. The

infection would appear obviously to have been the same. Imagine, therefore, the irritation and chagrin of the patient, to say nothing of my utter dismay, when this drug had no effect whatsoever and finally I had recourse to the old A.P.C. four-hourly with fluids plus, which did the trick! But he didn't shoot!

I can only briefly touch on the question of after-treatment, and this naturally depends on the severity of the condition and as to whether complications have occurred. In many simple cases I find convalescence is quite prolonged, but with the judicious and general use of stimulants, hæmopoietics, and the vitamins, the debility and depression gradually pass away. Naturally if there have been complications, the picture is entirely altered.

I would like so much to hear the views of those at this Meeting as to whether it is their opinion that there has been much headway in the treatment of influenza. Going back over a survey of over twenty-five years of practice, I am reluctant to state that in my experience there has been little progress in this long time.

As regards the graver types and the various complications, I am hoping Sir Horace Evans and Dr. Andrewes will say something of these. I have mentioned only briefly in this penultimate part of my paper, these questions of types of infection and treatment entirely from a General Practice point of view.

To sum up:

(1) Influenza differentiates between neither palace nor humble cottage.

(2) Definite diagnosis is still lacking.

(3) There would appear yet to be no drug whose response is certain in all types.

(4) It is still unpredictable when complications will arise.

(5) Probably owing to the toxicity, convalescence is prolonged in many cases, out of all proportion to the severity of the attack.

(6) Little progress has been made so far, over many years in the prevention and eradication of the disease.

Sir Horace Evans: We must surely all agree that Dr. Scott has given us an excellent survey of the problem based on personal practical experience—touching on pertinent points in diagnosis, complications, prognosis and treatment. Perhaps of these the problem of diagnosis is the most important and it is on this that I would like to speak.

It is necessary to remind ourselves of the clinical features of influenza itself and of the disorders which may closely simulate it in their early phase. Though it is known that true epidemic influenza is due to a filtrable virus, that antibodies appear in the blood, and that immune serum can prevent experimental infection in ferrets and mice, there is a big gap between these discoveries and their effective application to the treatment of human sufferers. The disease is endemic throughout the world. There have been eight great pandemics since 1510, the illness occurring in three waves, the first extensive but mild or moderate and the subsequent waves of a more severe type. The onset is very sudden, and the spread to others rapid. In a few hours a whole household can be laid low. Sir Thomas Watson said that when he was first called to two cases on April 3, 1833, the symptoms were just those which frequently mark the commencement of an attack of continued fever and that he did not then know what was about to happen; but in the course of that and the following day all London was smitten by the disease.

A fair statement at present would be that influenza produces general toxæmia and inflammation of the mucous membranes of the upper respiratory tract; the severer the attack the more likely is the inflammation to descend to the trachea and bronchi, and even to become hæmorrhagic. The onset of the illness is sudden, with fever, headache, shivering, muscular pains and prostration—there may be photophobia and abdominal pain. The pulse and respiration rates are quickened and in a couple of days catarrhal manifestations occur in the respiratory tract. The fever in an uncomplicated

case persists for about four days, is remittent and often diphasic. This is the usual picture of the disease in the first wave, but in the second and third waves broncho-pneumonia of varying severity complicates. Convalescence is usually slow, post-influenzal bradycardia, depression and polyneuritis often being residual features.

The mild case may be confused with a number of other maladies, but in particular the common cold or febrile catarrh. This is an acute catarrhal inflammation usually beginning in the nose and apt to spread to other parts of the respiratory tract. It is due to a filtrable virus and is followed by secondary infection. There is usually fever, shivering, depression, body aches and upper respiratory discomfort, but the pulse and respiration rates are not affected and the fever lasts only a day or two. Poliomyelitis, encephalitis, measles, whooping cough and enteric fever are febrile illnesses accompanied invariably by catarrh of the respiratory system. In measles the Koplik's spot and in whooping cough the vomiting may make the diagnosis clear. In the enteric fevers, apart from the slow pulse, minimal bronchitis and a degree of apathy due to slight deafness may be helpful in the diagnosis.

Glandular fever, infective hepatitis and the atypical pneumonias are other disorders due to virus infection which may be difficult of diagnosis. The onset in these is usually insidious and not sudden, and the pulse-rate is slow. In glandular fever, sore throat, headache, photophobia and conjunctival injection precede the more characteristic features. In infective hepatitis anorexia is pronounced from the outset and there is often hepatic pain on effort; the darkened urine may be obvious before jaundice is certain. The atypical pneumonias present a difficult problem because there may be a complete absence of physical signs. A tiresome, tickling, non-productive cough is typical. As we may hear from Dr. Andrewes, several types of this disease are now being recognized and some may be proved by the presence of certain agglutinins.

Meningococcal meningitis and Weil's disease may be confused with the more severe types of influenza. In the former, the early neck rigidity and rash often first seen on the soles of the feet may clarify the diagnosis. In the latter, hæmorrhagic herpes may be diagnostic.

Clearly a diagnosis of influenza may be the label for any pyrexia of uncertain origin, though such is to be deprecated certainly in most instances and even in most of the conditions I have mentioned. An appreciation of the sudden onset of influenza, and of the early indications of the other disorders which resemble it, should help to avoid mistakes in diagnosis.

Dr. C. H. Andrewes: I feel sure that the general practitioner can help to unravel some of the mysteries of influenza. It is first of all necessary to be sure what disease we are discussing.

We know more about influenza A virus than about most viruses. I have been working with this virus for eighteen years this month and was therefore surprised to hear from Dr. Scott that there is a textbook of medicine which refers to influenza as "a disease of doubtful ætiology"—I hope this is not a recent edition. We have to distinguish between "clinical influenza"—a term of convenience applied to short febrile diseases—and influenzas A and B, epidemic diseases due to known viruses. These can be distinguished from diseases simulating them—what may perhaps better be called "febrile catarrhs"—in three ways: Epidemiologically by their high incidence, clinically by their sharp onset and the predominance of general over local manifestations and in the laboratory by isolating the virus or by relatively simple serological tests. Clinically the diagnosis of small numbers of cases is difficult, but the practitioner seems to do it uncannily well when he signs a death certificate. For we can tell when viruses A and B are about by the weekly return of deaths from influenza in

the great towns—when this figure gets over 150 we are certainly up against virus influenza, when the figure is over 300 we are pretty sure it is virus A and not B.

Dr. Scott mentioned the abdominal type of influenza and hoped I would refer to it. I will. I suppose he means so-called gastric 'flu. We have repeatedly sought and failed to find evidence that epidemics of gastric 'flu have anything to do with the influenza viruses. Gastric 'flu may be a convenient term but it is misleading and should be dropped. A year or two ago an article in the medical press drew entirely unjustifiable conclusions on epidemiology through assuming that a gastro-intestinal outbreak following on true influenza was part of the same picture. If the seductive but deceitful name "gastric 'flu" had not been so prevalent, this mistake need not have been made. Can it not be called "epidemic gastro-enteritis"—a name surely more impressive and satisfying to the patient?

A word about therapy—aureomycin and other drugs are not of value in experimental influenza in animals; we know no drug that is. Influenza in man is usually a short self-limited infection and I know of no evidence that when it is uncomplicated any medicine specifically affects its course. [I do not refer of course to use of drugs given for relief of symptoms. If a fatal 1918-type of pandemic comes again, antibiotics will, we hope, save many lives. But let us not be too confident. Some fulminating cases in 1949 due to combined action of influenza A and staphylococci were not saved by penicillin.]

I now turn briefly to epidemiology. We have learnt a lot in the last few years by studying the epidemiology of 'flu on a world-wide basis. At Mill Hill we have, with this end in view, a World Influenza Centre working under the World Health Organization. One thing it has thrown up is this: 'flu is apt to get going in the autumn or early winter in localities where localized outbreaks have occurred in the previous May and June. In 1943 that happened in Britain, Canada and the U.S.A. In 1949 it happened in Sardinia and an epidemic spread thence all over Western Europe to Iceland. In June last year there was 'flu around Stockholm. We thought therefore that things might start this autumn in Scandinavia. We incited Dr. Svedmyr in Stockholm to look out sharply for what might happen in Sweden and we also got the State Serum Institute in Copenhagen to make an experimental batch of vaccine against the summer Swedish strain. Sure enough, 'flu did start up in November in Denmark, Sweden and Norway. The outbreak in this country, especially around Newcastle, in December strongly suggests importation from Scandinavia, though that starting in Liverpool may have come from elsewhere. Despite his best efforts Dr. Svedmyr could not detect any 'flu virus in Sweden, either in man or any possible animal reservoir, between June and November. Yet it must have been somewhere, for our serological studies show that a strain from Copenhagen in November was of the same antigenic sub-variety as the June Sweden one. We suspect it can, for a matter of months, go underground, possibly infecting some other species, more probably lying dormant somewhere in human hosts till something activates it with the onset of cold weather. This is where the G.P. can help—first by informing us or the Ministry of occurrence of local outbreaks of possible 'flu when they occur in May and June; second, by keeping his eyes open for some clue which might help us to unravel the mystery of where 'flu goes in the summer time.

Section of Surgery

President—Sir STANFORD CADE, K.B.E., C.B., F.R.C.S.

[*December* 6, 1950]

DISCUSSION ON THE OPERATIVE AND CONSERVATIVE TREATMENT OF PERFORATED PEPTIC ULCERATION

Mr. Digby Chamberlain: The treatment of perforated peptic ulcers has gone through several phases since opening the abdomen became a practical possibility, but in all of them closure of the perforation has been the basic principle. During the heyday of gastro-enterostomy for duodenal ulcer, this operation was carried out extensively for perforation and in my own hospital it was almost the routine if the patient was judged well enough to stand it, whether a stenosis was present or not. Later, when the results of a short circuit began to be questioned, it was dropped and is now only employed in the presence of a stenosis. With increasing experience the surgeon has come to realize that the swollen, œdematous duodenum which he may find at the time of operation is not necessarily stenosed and that it may become quite adequate when the acute process has had time to settle down. It is true that the longer the history before operation the more likely is it that symptoms will recur, probably because the ulcer is larger and more chronic and more likely to be associated with some narrowing. Illingworth *et al.* (1946) reported 10 gastro-enterostomies in 880 cases.

For some years Continental surgeons have advocated partial gastrectomy for perforation if the patient is in reasonably good condition but in this country the general view is that operation for a perforation is a life-saving measure and that radical treatment should be reserved for a later period and only if the symptoms call for it. For this reason the number of gastrectomies carried out has been small and we have to go to Continental clinics for statistics.

Lastly the conservative treatment of perforations is a method which has been advocated in recent years.

It is important to examine the results from these various forms of treatment, for our practice must depend on them. Apart from diagnosis itself, there are certain points of interest.

Strang and Spence (1950) found 177 perforations in men and 12 in women, and comparing these with Tidy's (1945) figures of 3·6 to 1 for non-perforated ulcers they pointed out that an ulcer in a woman is less likely to perforate than that in a man.

Luer (1949) reporting on 362 cases found that 4·7% were in women. Tidy (1945) also came to the conclusion that an ulcer is more likely to perforate in a man than in a woman. He found that 19·1% of duodenal ulcer admissions were for perforation and 12·1% of gastric ulcer admissions, and he pointed out that this showed that a duodenal ulcer is more likely to perforate than a gastric ulcer.

Illingworth *et al.* (1946) found that 87% of perforations were duodenal and that 95% of perforations were in men.

Luer (1949) found that in patients with free gas demonstrable on X-ray there was a mortality of 20·2% and if gas could not be seen it was 14·8%. A disturbing finding in his series was that in patients perforating while in hospital there was a mortality of 100%.

All authorities are agreed that posture, physical activity and the stage of digestion have no bearing on perforation which is an unpredictable complication. The stage of digestion may have some bearing on peritoneal soiling and therefore on prognosis.

Strang and Spence (1950) and Luer (1949) find perforations are commoner in the afternoon and evening and that there is a rise in incidence in the spring and a fall in the autumn.

Luer (1949) finds that if the perforation is 1 cm. in size or larger, the mortality is 33·3% whereas in smaller perforations than this it is 14·4%. The statement that a perforation cures an ulcer has no foundation on fact. 50% of Grey Turner's patients have had further symptoms; and Finsterer advises every patient who has not had a primary gastrectomy to return in three months so that this can be carried out. Sallick found that 71% of patients had a persistence of their symptoms after operation. Forty (1946) found that of 83 patients, 10 had operations later, 1 for a perforation, and 2 of them died. Illingworth *et al.* (1946) found that 40% of patients had symptoms in the first year and that by the end of five years 70% had had further trouble. He estimated that year by year 2% reperforate, 1% bleed and 2% elect to undergo operation. Of 666 cases in five years, 11 died, 7 from reperforation and 4 from further operation. He found that the older age-groups were more likely to be symptom free and that the long-standing ulcers were more prone to give rise to trouble. Strang and Spence (1950) suggest that the longer an ulcer is present, the more likely is it to perforate.

Recurrent perforation is reported in 4% of 300 cases by Cohn (1941), in 11·6% of 189 cases by Strang and Spence and in 4·1% of 362 cases by Luer. It is said by Cohn that there is a lower mortality for recurrent perforations, possibly because the area may be sealed off, or possibly because the patients, having already experienced this catastrophe, make their own diagnosis and come to hospital earlier.

Sangster (1948) reported 100 perforations up to 1939 with 24 deaths and 105 up to 1948 with 4 deaths. He attributed the improvement to better anæsthesia and more effective post-operative care including the antibiotics.

Luer (1949) found a mortality of 10·6% in cases operated upon up to six hours, 25·4% between six and twelve hours, 52% between twelve and twenty-four hours and 75·9% over twenty-four hours. Tidy (1945) found an overall mortality of 22%; in duodenal ulcer 19% and in gastric ulcer 24·6%.

Illingworth in 880 cases found a mortality of 17%, and Forty (1946) also had a 17% mortality in 100 cases.

Forty in his 100 cases had 39 chest complications, 2 empyemas and 2 subphrenic abscesses.

Luer found post-operative complications in 24·4% operated on in the first six hours and in 72·7% after twenty-four hours.

The figures (Table I) from my own hospital, the General Infirmary at Leeds, are for the twenty-year period 1930–49 during which time there were 1,622 admissions for perforation. Of these 1,526 or 94·08% were in men. An analysis (Table II) of the various types of ulcer

TABLE I.—TOTAL CASES FOR THE TWENTY-YEAR PERIOD 1930–49

Total cases	1,622	
Males	1,526	94·08%
Females	96	5·92%

TABLE II.—FIRST TWO COLUMNS SHOW THE FREQUENCY OF THE VARIOUS TYPES OF PERFORATION, THE LAST FOUR COLUMNS SHOW THE SEX INCIDENCE IN EACH TYPE OF PERFORATION

	Total	%	M.	%	F.	%
Gastric ulcer	147	9·06	115	78·23	32	21·77
Duodenal ulcer	1,436	88·53	1,374	95·68	62	4·32
Anastomotic ulcer ..	26	1·60	26	100	0	0
Pyloric ulcer	10	0·62	9	90	1	10
Carcinoma	3	0·18	2	66·66	1	33·33

shows that the only departure from the overall figure is that gastric perforations appear to be relatively more common in women although they are still actually more frequent in men in the proportion of 4 to 1. From a study of the age at which they occurred it is apparent that the 40–50 decade shows the highest incidence of all kinds of perforation (Figs. 1, 2 and 3).

I have analysed the incidence year by year and except for the low figure for 1947 this shows nothing of special note (Fig. 4).

A study of the time of admission shows that 76% of cases are admitted in the first nine hours. It also shows that women are admitted on the average later than men, probably

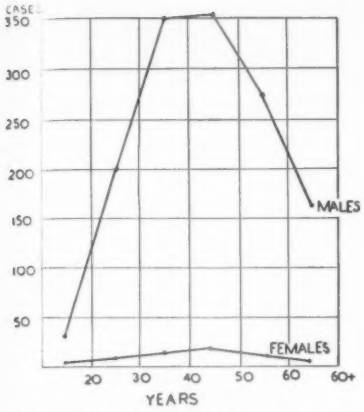

FIG. 1.—Age incidence in 1,436 cases of perforated duodenal ulcer.

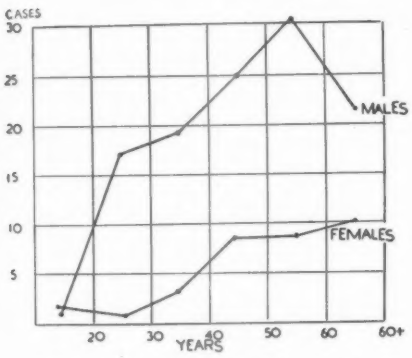

FIG. 2.—Age incidence in 147 cases of perforated gastric ulcer.

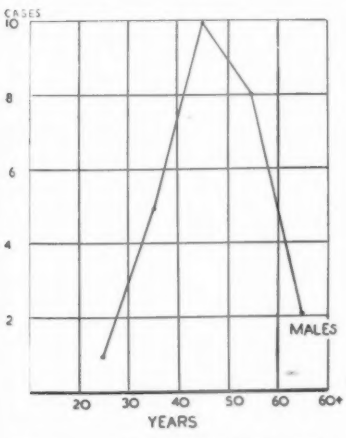

FIG. 3.—Age incidence in 26 cases of perforated anastomotic ulcer.

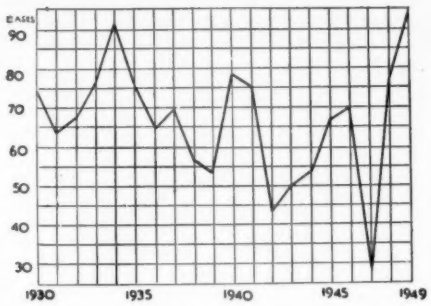

FIG. 4.—Incidence of cases year by year.

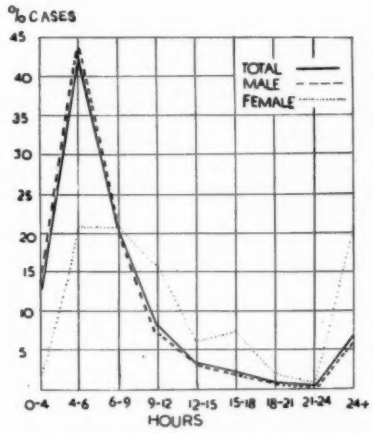

FIG. 5.—Graph showing the percentage of cases admitted at varying intervals after perforation.

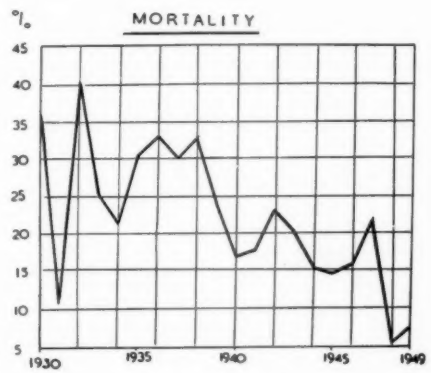

FIG. 6.—The percentage mortality for all types of ulcer year by year.

because the condition is rarer in them than it is in men and therefore the diagnosis does not enter the doctor's mind quite so readily. This fact probably explains the higher mortality in women which occurs in this series and in all other reported series of cases (Table III; Fig. 5).

TABLE III.—TIME OF ADMISSION

Hours	Total	%	Males	%	Females	%
0–4	215	13·25	212	13·89	3	3·16
4–6	685	42·23	665	43·54	20	20·91
6–9	344	21·21	324	21·22	20	20·91
9–12	130	8·01	115	7·51	15	16·04
12–15	56	3·45	50	3·25	6	6·32
15–18	38	2·34	31	2·03	7	7·38
18–21	28	1·72	26	1·73	2	2·24
21–24	15	0·92	14	0·90	1	1·12
over 24	111	6·87	89	5·93	22	21·92

An analysis of the time of admission by age-groups makes it apparent that the younger age-groups are operated on rather earlier than are the older patients (Table IV).

TABLE IV.—SHOWING THE TIME OF ADMISSION AFTER PERFORATION FOR THE DIFFERENT AGE-GROUPS (%)

Age	Total Hours	0–4	4–6	6–9	9–12	12–15	15–18	18–21	21–24	24+
0–20	2·04	3·27	1·61	1·75	1·54	6·89		7·14		0·92
20–30	14·12	20·56	15·27	11·40	8·46	17·24	10·53	17·86	13·33	8·25
30–40	24·33	36·45	27·17	21·87	11·54	17·24	18·47	17·86	20·0	13·76
40–50	25·56	21·49	27·02	25·28	33·08	17·24	21·05	25·0	26·67	21·1
50–60	21·11	14·48	18·94	23·68	25·38	24·15	36·84	14·28	26·67	28·44
60+	12·84	3·75	9·99	16·02	20·0	17·24	13·11	17·86	13·33	27·53

The previous history has also been gone into and demonstrates that 30% had no previous trouble, 2·59% were recurrent perforations and 1·85% had previously bled (Table V).

TABLE V.—PREVIOUS HISTORY

	Cases	%
Symptoms	1,035	63·81
Nil	487	30·02
Hæmorrhage	30	1·85
Gastric operation	28	1·73
Perforation	42	2·59

The mortality for these twenty years was 17·94 % but in women the figure is 27·66 %, a matter on which I have already commented. Thus, perforations in women carry a higher mortality in every type of ulcer, and gastric ulcer has more than twice the death-rate of duodenal ulcer (Tables VI and VII).

TABLE VI.—THE MORTALITY FOR ALL TYPES OF PERFORATION

	Died	%
Total	291	17·94
Males	265	17·34
Females	26	27·66

TABLE VII.—THE MORTALITY FOR PERFORATION OF THE VARIOUS TYPES OF ULCER

		Total	Died	%
Gastric		147	52	35·37
	M	115	40	34·78
	F	32	12	37·5
Duodenal		1,436	227	15·81
	M	1,374	214	15·57
	F	62	13	20·97
Anastomotic		26	10	38·46
	M	26	10	38·46
Pyloric		10	0	0
	M	9	0	0
	F	1	0	0
Carcinoma		3	2	66·66
	M	2	1	50
	F	1	1	100

The mortality year by year for all cases shows a considerable amount of fluctuation but it does show a gradual reduction, particularly in the past two years, due almost certainly to the routine use of the antibiotics. On an analysis of the figures there is no evidence that cases are admitted earlier now than they were in 1930 (Fig. 6).

The operative details and mortality have been analysed (Table VIII). Simple suture carries the best result and is certainly related to the condition of the patient rather than the type of treatment. Where a drain had to be used the death-rate was over four times as great

TABLE VIII.—METHODS OF TREATMENT CARRIED OUT SHOWING THE MORTALITY FOR EACH TYPE OF OPERATION

	Total	%	Died	%
Suture and graft	932	57·46	69	7·40
Suture and drainage	515	31·75	165	32·04
Suture and gastro-enterostomy ..	111	6·86	18	16·22
Suture and jejunostomy	14	0·86	4	28·57
Pyloroplasty	6	0·37	0	0
Drainage only	20	1·23	15	75
Nil	24	1·48	20	83·33

but this means that a peritonitis was already present. Gastro-enterostomy probably takes in a mixed group, some of them may have been done as a matter of principle and some because there was a stenosis and it is probably this latter group, occurring in ill patients, where it was considered necessary to carry it out in spite of the general condition of the patient, which accounts for the mortality of 16%. Jejunostomy and pyloroplasty represent phases and their numbers are too small to be worthy of comment. When drainage only was possible the mortality was 75% and where nothing was done, usually because of the poor general condition of the patient, the mortality was 83%.

A comprehensive table has been worked out for the age of the patient and the lapse of time since the perforation and confirms the known facts that these two factors operate adversely on the result (Table IX).

TABLE IX.—% MORTALITY BY AGES AND HOURS

Comprehensive table showing the percentage mortality for the various age groups, according to the time of admission after perforation.

	Hours—									Any
Ages	0–4	4–6	6–9	9–12	12–15	15–18	18–21	21–24	24+	time
0–20	0	9	17	0	67	0	0	0	100	15
20–30	5	2	3	18	20	0	40	0	44	6·5
30–40	2·7	2·7	10·6	15	20	14	80	100	13	7·3
40–50	8·7	6·5	13·5	21	50	37	14	25	50	14
50–60	22·5	21·6	20·7	30	50	28	25	25	64	28
60+	37·5	33	25	41	50	80	60	50	86	42
All ages	8·4	10·5	14·9	26	38	31	39	40	58	

The post-mortem findings show that peritonitis is the commonest cause of death and is likely that this figure has been reduced in the past year or two, but the numbers available for study are not sufficient to bring out this point (Table X).

TABLE X.—COMPLICATIONS FOUND POST MORTEM

Peritonitis	205
Chest	92
Burst abdomen	9
Obstruction	6

I have collected the serious operative complications as they were noted (Table XI).

TABLE XI.—POST-OPERATIVE COMPLICATIONS IN THE NON-FATAL CASES

Subphrenic abscess	16
Pelvic abscess	4
Burst abdomen	11

The subsequent history has been obtained from 56% of the survivors and shows that nearly 4% have reperforated and that in addition 14% have had to undergo a further operation. 33% have symptoms which cause them to have time off work or call for treatment, but operation has not been considered necessary. 7% have died of other causes and 2% have died of causes connected with their ulcers. 39% are apparently in normal health and free from symptoms (Table XII).

TABLE XII.—SUBSEQUENT HISTORY AT INTERVALS FROM THE TIME OF OPERATION IN 748 CASES FOLLOWED UP

	1,331 survivors.	748 traced. 56%					
Years	6/12	1	2	5	10	20	Total
Operation—							
Perf.		4	4	12	5	3	28
Gastro-enterostomy ..	3	4		7	1	1	16
Gastrectomy	13	22	7	20	12	12	86
Vag.	2		1	1			4
Symptoms		34	21	39	70	87	251
Symptom free		43	22	44	96	89	294
Died of other causes ..	5	2	4	11	13	19	54
Died of ulcer	4	2	1	4	4		15
						Total	748

PARTIAL GASTRECTOMY

First of all it is necessary to compare cases of the same type and it will be agreed that gastrectomy is only carried out in patients who are well enough to undergo something more than the minimum treatment; for this reason we can compare the results with perforations sutured in the first nine hours. In addition we must take into account the secondary mortality occurring when a subsequent gastrectomy is carried out or when a second perforation takes place. Even this is perhaps not quite fair as it makes no allowance for the morbidity which occurs in the group who continue to complain of symptoms but who do not undergo a second operation.

Yudin was reported by Cohn in 1941 as having a mortality of 12·8% in 426 resections and in a personal communication this year Nuboer had 105 resections with a mortality of 3·8%. This second series, of course, should be more favourable because of the improved post-operative treatment in recent years.

Sutured perforations without drainage carried a mortality of 7·4% during the twenty-year period and if to this we add 1·65%, a figure based on Illingworth's 11 deaths in 666 cases, we arrive at a figure of 9%, or if we take the figure of 2·5% which is the mortality when suture has been carried out in the past few years and add to this the figure of 1·65%, we get a total of 4·15%, so that this is the figure we have to compare with the results of gastrectomy. I hesitate to recommend partial gastrectomy on a wide scale but if we take Nuboer's figure of 3·8%, it suggests that the experiment might be worth making in one or two centres when the treatment itself and the results can be carefully controlled.

ANALYSIS OF RESULTS

Simple suture has given the best overall results with a mortality of 7·4% for the twenty-year period. Gastric ulcer carries more than twice the mortality of duodenal ulcer. The gross mortality has been reduced to about 6% in the past two years, this is due to chemotherapy, the antibiotics and more efficient anæsthesia and not to earlier diagnosis. Finally the mortality in women is higher than in men, due to delay in diagnosis, a fact which I do not think has been previously brought out.

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Mr. Hermon Taylor: Until recently, there has been no alternative to the practice of immediate suture of perforated ulcers, despite all risks and hazards. For many surgeons, however, the technical satisfaction of this operation has been tempered by the overall results, which up to 1945 showed a mortality of 15–20%. The disquiet of many who have contemplated this has not been eased by the realization that death has mostly been due to the complications of the operation itself. These are mainly respiratory or cardiovascular conditions, sepsis or intestinal obstruction, and though their incidence has been reduced by modern techniques and drugs since 1945, the mortality and morbidity after operation are still considerable in ill or elderly subjects. It is important therefore to remember Heroclitus' teaching that nothing is permanent except change, and to review our methods in the light of recent new facts. The most important of these are the antibiotics, and the spontaneous sealing of a perforation when the stomach is empty. Wangensteen was the first to apply the latter in his continuous gastric suction treatment of patients with late perforations which had already sealed, but who still suffered from peritonitis and ileus.

The therapeutic possibilities of this method in early cases have now to be considered. The peritoneal contents remain sterile for several hours after contamination from a perforation, and the object of operation in these circumstances is to stop further spillage of gastric contents, and thereby forestall a fatal peritonitis. Clearly it should be possible to achieve the same effect more simply by keeping the stomach empty by repeated aspiration of the contents. This is so, in actual fact, and cases have been treated on this principle at King George Hospital, Ilford, since 1944. The technique will be described by Mr. J. F. R. Bentley, who with Mr. C. P. Allen has been in direct charge of most of the cases.

The results up to 1946 were 28 cases with 4 deaths—2 inevitable and 2 due to mismanagement—but nevertheless better than the surgical mortality (18%) at the hospital at that time. We therefore continued to treat our acute perforations by aspiration unless severe infection had already developed, or unless we were in doubt about the diagnosis. With experience, we have acquired confidence in the early non-infected cases, but in the later cases with peritonitis and toxic absorption we have been impressed with the necessity to remove the toxic fluid from the peritoneal cavity. We therefore operate on these patients in order to drain the abdomen: if conditions permit, we carry out the classical suture of the perforation and peritoneal toilet, but in desperately ill cases we drain the pelvis and renal pouches under local anæsthesia, and rely on the gastric tube to prevent further peritoneal infection. Frequently the latter provides an additional channel of drainage of the peritoneal cavity, the gastric aspirate being at first identical with the discharge from the abdominal drainage tubes.

We have encountered one major pitfall—air-swallowing. The swallowed air does not escape readily from a small tube, but tends to pass through the perforation, which is thereby prevented from sealing by adhesion to a neighbouring viscus. This fact was not appreciated until 2 patients in our second series had died from peritonitis after seven days. All patients are now X-rayed on the second day, and if an increase of intraperitoneal gas is found, the abdomen is opened. 2 further patients have since been dealt with in this way and have done well. The position is still *sub judice*, but there appears to be no danger from the passage of air into the peritoneal cavity, provided the fluid contents of the stomach are withdrawn and operation is undertaken within thirty-six hours.

Our second series of cases at King George Hospital has consisted of 73 cases, and two fatalities have thus occurred as a result of mismanagement through inexperience. There have been 5 other deaths—3 moribund patients perforated over twenty-four hours, 1 patient in irreversible shock, and another who died from pneumonia, having both contracted and resolved his perforation in the course of this disease. None of these 5 patients could have been saved by operation, even had this course been possible. Among the survivors, we have had the satisfaction of seeing 7 cases of acute respiratory disease and others of coronary disease, phthisis and uræmia recover, despite their unsuitability for operation.

In addition to the 73 true perforations, there were 4 instances in which other acute conditions were wrongly diagnosed as perforations and treated by aspiration. An acute gall-bladder and a basal pneumonia with pleurisy both subsided; a perforated appendix did well after intercurrent operation: a perforated right colon (? diverticulum) died. In the latter case operation was delayed by two and a half hours' aspiration—a serious error, but not the decisive factor in so universally fatal a condition. The advantage of avoiding operation in the case of pleurisy diagnosed as a perforated ulcer may perhaps be set against this, and on balance it may be said that clinical error has not in this series been found to defeat the object of our experiment.

The aspiration method is being investigated by several workers on the Continent and in America, to some of whom I am indebted for their special permission to mention their unpublished results. Altogether I have been able to collect 411 cases with 33 deaths. Of these 15 had been moribund cases and 5 others had died of other diseases, having recovered from their perforations. Only the total figures are admissible for comparison, but it is worth noting that in the remaining operable cases the mortality of this untried method, in the hands of men with no experience of its pitfalls, but only their clinical instinct to guide them, has been as low as 3%. Our own mistakes have shown that these results can be improved, but clearly the hard core of moribund cases will persist.

I hope I have been able to make a case for the aspiration treatment of perforated ulcers. It raises new problems, but I feel it will take its place alongside operation in the management of this condition. There should be no question of competition between consecutive series of cases treated this way or that. Rather must there be a general policy, under which the advantages and disadvantages inherent in each method will determine the treatment in any particular case.

Mr. J. F. R. Bentley amplified some of Mr. Hermon Taylor's remarks: In the practical management of patients at King George Hospital, Ilford, a clinical diagnosis is made in the Casualty Department, and intravenous morphia then given. The throat is anæsthetized with an amethocaine lozenge, and the stomach emptied using a large bore stomach tube and Senoran's bottle. This tube is replaced by a smaller one of radio-opaque rubber, and a plain X-ray of the abdomen in the erect posture is then taken. The film is examined to see (i) if the tube is in the stomach, (ii) if the stomach has been emptied and is free of gas, and (iii) how much, if any, subphrenic gas is present. A second film is always taken twelve hours later; if this shows more subphrenic gas, there is a persistent leak, which must be remedied by operation.

The stomach is kept empty for twenty-four hours by absolute starvation and gastric aspiration at fifteen-minute intervals. It is important to test the tube at each aspiration by injecting and *recovering* 2–3 ml. of water. The next day, sips of water are allowed and aspiration is less frequent. On the fourth day the tube is removed and an ulcer diet started. Salt and water balance are maintained by appropriate measures and pain is controlled by morphia. Uneventful recovery is usual, and full investigations are undertaken before discharge in the third week.

The special dangers associated with the method are those of misdiagnosis and persistent leakage. Dangerous misdiagnosis is rare in practice, the errors being rapidly detected by the relatively poor response to the initial treatment. Operation is undertaken in all cases of doubt.

The commonest complication is chest infection, notwithstanding the lack of anæsthetic or operation, and patients therefore receive penicillin. Intraperitoneal abscesses are not frequent.

65% of the patients have shown subphrenic gas on X-ray. This corresponds with the experience of McElhinney and Zinniger (1950, *Arch. Surg.*, **61**, 758) in a large series in which the diagnosis was proved at operation.

Strict controls have not been kept, but the results obtained with conventional treatment over a similar period at Guy's Hospital and the London Hospital are considered of interest. The three series show remarkably little difference.

GASTRO-DUODENAL PERFORATIONS
TABULATED RESULTS

Hospital .. Date ..	Guy's 1946–49	London 1946–49	King George Sept. 1946–Sept. 1950
Number of patients	75	75	73
Perforations sutured	69	65	6
Treated by aspiration	4	7	65
Total deaths	7	10	7
Therapeutic misadventures	3	2	2
Recorded morbidity	30	20	14

Dr. E. W. Bedford-Turner: (1) When I first attempted the conservative method it was not to supplant operative treatment but to record that perforated peptic ulcer could be cured by conservative treatment—namely with two pieces of rubber tubing one in the stomach and the other in the rectum. This would be of help and reassurance to a doctor isolated from general surgery.

(2) I was first led to attempt this method when I noticed how often I had to remove the omentum which was sealing the perforation in order to suture it.

(3) It is necessary to have a skilled nursing team to carry out the conservative method of treatment—to carry out repeated gastric suction and to ensure adequate fluid balance.

(4) One cannot always be sure of the diagnosis unless the abdomen is opened.

(5) In view of the decrease in the operative mortality rate it is now my opinion that whereas the conservative method would be extremely useful where a skilled surgeon is unobtainable yet the ideal method is still to operate.

Mr. Ivor Lewis: I think we are all now very impressed by Mr. Hermon Taylor's results, the more so as he no longer advocates conservative treatment in the moderately late cases already developing toxic symptoms. It would be deplorable, however, if the discussion were to lead to its general adoption up and down the country, as the results, without the unremitting vigilance and enthusiasm described by Mr. Taylor, would be sure to be much worse than those of suture.

It is interesting to hear that as many as one-third of the Leeds cases denied previous indigestion. In my experience about half of such cases *have* had pain for a few weeks but have not known it as "*indigestion.*"

Mr. J. R. Stead: The results of 77 consecutive cases of perforated peptic ulcer admitted to Hackney Hospital were reported. These were grouped as follows:

		Number of patients	Died
Moribund on admission		5	5
Poor operative risks:	Conservative treatment	11	3
	Operative treatment	2	1
Good operative risks:	Conservative treatment	40	2
	Operative treatment	19	1
		77	12

The total mortality was 15·6% but when the moribund cases were excluded the mortality was 9·1%. This result compared favourably with the mortality of 18% in 80 cases treated by operation at Hackney Hospital during the previous three years.

The cases in which the conservative method had failed were briefly described, and the risk of operative treatment without an experienced anæsthetist was illustrated.

The limitations of the conservative method were admitted, and the following indications for operation were suggested: (1) Inexperience of the surgeon in the conservative method. (2) Unsatisfactory progress after six hours. (3) Doubtful diagnosis.

Neither the conservative nor the operative treatment should be used as a routine, but the indications for each method require further study.

Mr. Richard Doll: Dr. Avery Jones and his colleagues in 1950 (*Brit. med. J.* (i), 211) published a series of 490 perforations treated at the Central Middlesex Hospital in the period 1938–48. A steady reduction took place in the mortality and, out of the last 106 cases operated on, 4 died. Since then our experience has been similar. Since the beginning of 1948 169 patients have been admitted to the Central Middlesex Hospital with perforated peptic ulcers. In 9 instances the patients could not be resuscitated sufficiently for operation or the diagnosis was not made until autopsy; the other 160 patients were treated by suture or partial gastrectomy and 3 died. With an operative mortality of the order of 2% conservative treatment is, in our opinion, only indicated: (1) When surgery is not readily available; (2) when associated conditions, e.g. coronary thrombosis, greatly increase the risk of surgery; (3) when the perforation occurs in a completely empty stomach, e.g. at gastroscopy.

One advantage of surgery is that it permits partial gastrectomy to be undertaken in selected cases. A high proportion of patients with perforated ulcers have severe recurrent symptoms in the succeeding few years and, when the history is such that indications already exist for gastrectomy, it is reasonable to consider it at the time of perforation. It must also be remembered that an appreciable proportion of the deaths from perforated ulcers occur a few days later from hæmorrhage from the same or other ulcers; these deaths should be preventable by gastrectomy. More important, however, is the risk of carcinoma in perforated gastric ulcers. One hundred of the perforations treated surgically at the Central Middlesex Hospital between 1938 and 1948 were considered at the time of operation to be perforations of benign gastric ulcers and the patients were discharged from hospital under that diagnosis. 7 of these patients died of carcinoma of the stomach within the succeeding three years. An eighth case is of particular interest. The patient was found to have a perforation of the greater curvature which, at operation, was thought to be benign despite the rarity of benign ulcers in that region. He was followed gastroscopically for two months without any lesion being detected but six months later died of an oat-cell carcinoma of the bronchus. Autopsy showed that there were widespread secondaries including a small polypoid tumour, of the same histology as the main bronchial tumour, on the greater curvature of the stomach; no other gastric lesion was present. This case illustrates clearly what we believe may be a not infrequent sequence of events. An early carcinoma may produce a *locus minoris resistentiæ* in the gastric mucosa which may serve as the origin for an ulcer to be produced by peptic digestion. The peptic digestion may then continue until a perforation is produced when it will be extremely difficult, if not impossible, to recognize that a small carcinoma is present intragastrically in relation to what appears to be an ordinary simple ulcer. We, therefore, consider that partial gastrectomy should, under suitable conditions, be adopted as the treatment for perforated gastric ulcers.

Section of Physical Medicine

President—W. YEOMAN, M.D.

[*November* 8, 1950]

Hydrotherapy and its Place in Modern Medicine

PRESIDENT'S ADDRESS

By W. YEOMAN, M.D.

THERAPEUTICS have made rapid and dramatic advances since the last Presidential Address was delivered before this Section on the subject of Hydrotherapy by Geoffrey Holmes, in 1936. This is particularly so in the case of electrotherapy. The tendency is, therefore, to disregard some of the older and well-tried methods of treatment and substitute "new lamps for old". This is true of hydrotherapy, the oldest form of medical treatment. The Hindu Physician, Susruta, once said, "He who knows only one brand of his art is like a bird with one wing" and I consider this truism is an additional justification for studying this subject.

The history of the use of water as a therapeutic measure was then traced by Dr. Yeoman through the centuries from the earliest records of Egypt, Babylonia and Greece. It was noted that water was regarded as the universal purifier and therefore used in various religious ceremonies and in certain forms of trial as a test of innocence. The universal belief among primitive peoples that disease is due to evil influence and that water would wash away the evil was responsible for many of the old bathing rituals.

The types of thermal establishments used in Greece and Italy were described and the views of Hippocrates on the use of water in disease were noted. This part of the lecture was illustrated by slides taken from old woodcuts and line drawings.

The growth of Spas in Europe was described and it was shown how this affected the use of hydrotherapy in England. It was noted that the Spring at Epsom was the first source of Epsom Salts. After evaporating one gallon of Epsom water 2 drachms of impure magnesium sulphate was obtained and for many years this was sold for one shilling an ounce.

An extract describing a course of treatment undertaken at Gräfenberg in the late eighteenth century gave a vivid picture of the ritual of hydrotherapy founded by the Silesian peasant, Priessnitz. This vogue spread from the Continent to England and during the nineteenth century hydrotherapy reached its zenith in this country.

Dr. Yeoman then continued:

However, the gaining of more precise knowledge of the action of drugs and their more specific use started to make itself felt and the pendulum began to swing away from hydrotherapy. The advent of electricity accelerated this process and for the past twenty years

hydrotherapy as an effective therapeutic measure has been at least douched with tepid water if not actually subjected to the cold plunge.

I think one vital reason for this has been the attitude of the hydrotherapists themselves who have claimed specific action for the particular waters they prescribed.

Many attempts have been made to justify this attitude by scientific methods but few will stand up to critical investigation. Certainly various natural waters taken internally have an action on the body depending on their mineral content but so has a solution of these minerals made up by the pharmacist.

The difference in action on the body, if any, has never been satisfactorily investigated and until this is done the internal administration of natural waters must be classed as empirical. This problem of the effect of natural waters bristles with difficulties and the investigation on the action of the Harrogate Sulphur by Brown and Woodmansey (1929) as reported to the Section of Balneology in 1929 is a model which very few investigators have the time and patience to follow. This investigation showed the physiological action of sulphur water in normal subjects but no investigation has, so far as I know, been undertaken on its action in disease nor has the action of an artificially prepared solution been compared with that of the naturally occurring water. Until such investigation is undertaken for all natural mineral waters taken internally, the claims that these waters have a superior therapeutic action to that of pharmaceutical products cannot be scientifically substantiated. Medical history abounds in instances of natural products being used empirically for years and subsequently their use has been amply justified by scientific investigation. No doubt in course of time the internal use of certain natural waters for therapeutic purposes will likewise be justified.

We, in this country, are not making any effort to investigate the action of our waters but on the Continent there is considerable activity in this direction and I recently inspected a very well-equipped clinic at Montecateni, Florence, which is devoted entirely to the investigation of the action of the waters of that Spa.

I think it will be conceded by even the most severe critics that there is a certain empirical justification for the discriminate use of natural mineral waters internally for therapeutic purposes, but all will agree that used externally they produce their effect entirely owing to their mechanical and thermal properties.

A strict scientific investigation of the action of an immersion bath involves the worker in almost as many ramifications as in the case of the internal action of water but there are certain facts which can be accepted as proven which justify the use of baths for therapeutic purposes.

One-third of the entire blood content of the body can be contained in the peripheral circulation and therefore it is easy to understand that by a regulated course of baths at varying temperatures the resources of the skin may be so stimulated and reinforced that the sensitiveness of the patient to changes in external conditions may be materially lessened. The contrast bath is an example of this and the experiments of Collins and Woodmansey (1938) placed this treatment on a scientific foundation which has been carried still further by the work of Krusen (1950) and his collaborators.

The thermal effects of immersion baths at varying temperatures are too well known to be elaborated here but I would remind you of the mechanical effect which is of such vital importance in therapeutics. A body immersed in water is buoyed up by a force equal to the weight of water it displaces and the thrust upon the surface of a body immersed varies in direct proportion to the depth of the immersion. This buoyancy is used to enable still and paralysed joints to be moved actively through a greater range of movement and with less discomfort to the patient than is the case when the limbs are not so supported. The mineral content of the water here exerts its influence as is well shown in the case of Droitwich where the water is practically a saturated solution of sodium chloride having a density of ten times that of sea water. All highly mineralized waters are, therefore, of great value in assisting the rehabilitation of a disordered locomotor system.

It is this rehabilitation of the locomotor system which has been the main concern of hydrotherapists throughout the ages and is still their major problem to-day. The disease syndromes grouped under the generic term "Rheumatism" have, as I have shown, been treated by some form of hydrotherapy from earliest times and still respond to such treatment. Hydrotherapy acts on the patient as a whole and not particularly on an affected joint and the necessity for considering the patient as a whole and not as made up of disorganized joints is impressed upon us by the work of Selye and Hench and their collaborators. If we accept the theory that joint lesions are the result of stress whether that stress be due to mental, physical or bacterial causes, then we see what an important place hydrotherapy must take in protecting the patient against such stresses. "Disordered function is the disease; the tissue change a manifestation."

Just as the tepid bath was used in cases of dementia so in cases of rheumatism the bath of medium temperature in the range of 98°–100° F. (37°–38° C.) will give the patient more relief from muscle spasm in the simplest way. The water, in addition to its sedative thermal effect, acts as a buffer or body insulator and the more buoyant the water the more easily is a disorganized limb moved in the bath.

It is not enough, however, just to produce reduction in muscle spasm but it is also necessary to restore movement which has been restricted by this spasm and this can be started in the bath. From the simple immersion bath the patient can be graduated to the deep pool, or where that is not available the Hubbard tank, and from there to the Guthrie-Smith exercise machine. From there the progress is through the exercise class and the occupational room till finally mobility and independence is restored so far as is possible for each individual patient. Underlying this whole scheme should be individual attention to the patient as a whole, and the basic aim is to build up resistance to stress so that he or she is able to withstand future stresses with equanimity. The Spas of this country have been the pioneers of this scheme of rehabilitation and now that Spa treatment is recognized as a benefit which can be prescribed to a National Health Service patient there is no reason why their facilities should not be used to the fullest extent. Till recently the rheumatic patient received very scanty attention from the medical profession, except from the relatively few, but now that it has at last been realized how important this group of syndromes is to the economics of the country, interest and enthusiasm have been aroused, enhanced by the discovery of Cortisone. As Hench has pointed out, though Cortisone may control the acute and subacute stages there still remains the structural damage and it is in the treatment of such cases that hydrotherapy will still have a useful place.

I, therefore, feel that in the future each hospital of 200 beds or over should have a hydrotherapy unit incorporated in the physiotherapy department where ambulant patients can have periodic courses of treatment. The Spa hospitals should be reserved for the early and subacute cases requiring long rehabilitation where the patient can graduate from the specific medical treatment, via hydro- and physio-therapy, to active rehabilitation in surroundings which favour recovery—namely, quiet and peace—in other words general insulation. For the ambulant case regular courses of treatment should be encouraged and here the opening of hostels in connexion with the Spa hospital will supply a long-felt want. There patients can be housed while having their treatment at the municipal treatment establishment and in this way many convalescents and those suffering from the more chronic types of osteoarthritis can be rehabilitated more quickly than by remaining in their own homes and attending the large outpatients' clinics of a general hospital. I will conclude by quoting Plato, who said: "The limbs of the rustic worn with toil will derive more benefit from warm water than from the prescriptions of a not overwise physician."

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[*January* 10, 1951]

DISCUSSION: GOUT

Dr. Donald Wilson (Bognor Regis): *The Familial History of Gout.*

Many authors have contributed classical treatises on the subject of gout, from Sydenham in the seventeenth century to Sir Henry Cohen and Professor Wood Jones at the present time. Although the disease was described by the Hellenes the concise and satisfying term of "Gout" was first used in the thirteenth century when the secretary of the Bishop of Chichester applied the term to the disease of one of the Bishop's servants; a dramatic cure of the disease resulted from wearing the Bishop's boots. The Bishop was subsequently canonized but I do not think it was for lending his boots. St. Richard's Chapel still exists in Chichester Cathedral and the site of his tomb is known but I do not think that the inhabitants of West Sussex can be aware of the late Bishop's powers as I have investigated 77 cases of gout during the past two years in that county.

Although much has been written about gout the mechanism of the disease still remains one of the most intriguing questions in medicine.

The diagnosis of the 77 cases I present was based upon the criteria laid down by Kerr Pringle in 1922: (1) History of an acute attack. (2) Presence of tophi. (3) Hereditary history. (4) Hyperuricæmia. (5) Radiological findings.

Here, it is worth while noting that 14 of my cases had tophi (18·1%).

Out of 1,570 cases of arthritis and its allied disorders referred to me at three hospitals during 1949–50, I found 77 cases of acute and chronic gout (4·9%), a figure appreciably higher than that given by Hill in 1938 for the Royal Devonshire Hospital, Buxton; from the years 1921–35 his figures lay between 3·75% and 2·66%.

The hereditary factor has long been stressed as one of the most important ætiological points in the diagnosis of gout but it was not based upon this point alone. If no history of an acute attack could be obtained or a tophus was absent then the diagnosis was based upon a combination of articular signs and symptoms, high blood uric acid and radiological findings.

For several years I had observed that attacks of acute gout had a tendency to occur when the patient was mentally depressed or physically below par. I had decided at some time to investigate the familial histories of my patients to try and find out if the members of these families not only had attacks of gout but were also liable to psychosomatic disturbances. I had started on this attempt before Selye's lecture to the Heberden Society but after listening to his lecture I realized that all of the disorders which I was considering, except two, had been included in Selye's list of conditions (Selye, 1950) that were likely to be relieved by ACTH or Cortisone.

Similar investigations were carried out simultaneously on rheumatoid arthritis—a disease considered by many to be a psychosomatic disorder—and osteo-arthritis. In this last condition only osteo-arthritis confined to one joint, either the knee or hip, was investigated. Thus, the family history was compared with a so-called psychosomatic disorder and a condition resulting from injury, wear and tear or infection (Table I).

TABLE I.—FAMILIAL HISTORY IN

	77 cases Gout	109 cases Rheumatoid arthritis	97 cases Osteo-arthritis
Gout	30	7	8
Rh. A.	15	17	7
O-A.	7	6	15
Asthma	0	8	7
Hay fever	0	3	2
Peptic ulcer	16	9	7
Mental instability ..	8	17	9

From these figures it will be seen that the disease the patient suffers from is apparently the most prominent one amongst his relatives. In gout, from 77 cases I traced 30 relatives who also claimed to suffer from this disease; in osteo-arthritis from 97 cases I found 15 relatives suffering from osteo-arthritis, a surprisingly low figure. In the cases of gout it is of interest to note that I could find no relative with asthma or hay fever and I think that this finding is not true. I have used the term "mental instability" to cover the conditions variously termed, nervous breakdown, temperamental instability and neurasthenia and psychoneurosis, when the condition was severe enough to warrant medical treatment. The cases of rheumatoid arthritis appear, at first sight, to have more mentally unstable relatives than those suffering from gout or osteo-arthritis but these figures can only be used as a very rough guide because I do not know the total number of relatives for each disease.

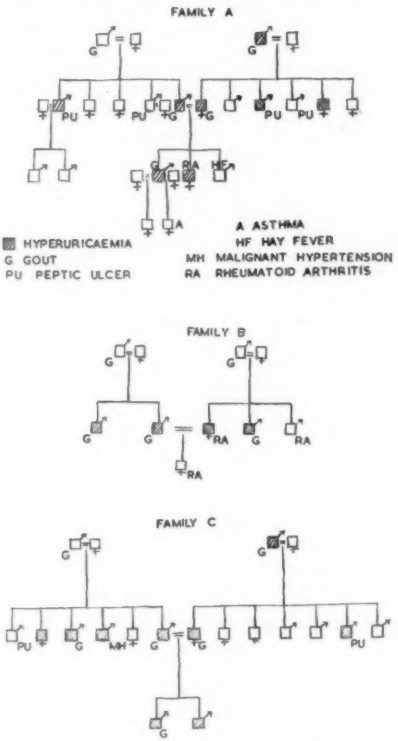
Reverting for a moment to the highest figures in each group, I think that patients are more likely to remember members of their families with a similar complaint and thus I was referred to them. Other members of the family who suffered from psychosomatic disorders of a different system might have been forgotten or my questions misunderstood. Other points worth noting are the relatively high numbers of rheumatoid arthritics and peptic ulcers in the families of the gouty.

I have also investigated three families for the above disorders.

Family A.—I have written to all the surviving members and to their medical attendants who have very kindly given me information. I was able to get isolated uric acid estimations carried out on 11 members of the first family, and of these 8 had a figure above 4 mg. % for the blood uric acid. These findings agree closely with Talbott's (1943) investigations but in addition, in the first family, I found 4 cases of peptic ulceration, 1 case of rheumatoid arthritis and 1 of asthma and 1 of hay fever.

Family B.—In the second family, out of 8 relatives examined, 4 had a high blood uric acid and 5 cases of gout were recorded; 3 cases of rheumatoid arthritis were found.

Family C.—The third family had 10 members examined, 9 of them had high blood uric acid (one of these suffers from malignant hypertension and the high blood uric acid is probably due to renal failure); they provided 6 cases of gout and 2 cases of peptic ulcer.



From these investigations it is suggested that members of families with a high blood uric acid may react to stress by developing gout but other members of the family may react by having stomach ulcers, rheumatoid arthritis or asthma.

In these investigations the estimation of uric acid has been of the utmost importance and with the help of pathologists I am carrying out a series of whole blood estimations on normal people and patients suffering from gout. A table of estimations is shown (Table II).

TABLE II.—WHOLE BLOOD URIC ACID MG./100 ML.

Date		8.12.50: B. male, 49	11.12.50: H., male, 60	12.12.50: D., male, 33	4.12.50: G. A. H., male, 57
Hours after breakfast	Breakfast	—	—	—	—
1¾		3·0	2·2	2·6	3·9
2¾		2·5	2·4	2·4	4·4
3¾		2·2	2·5	2·7	4·7
4½	Lunch	—	—	—	—
6½		2·2	2·2	2·6	4·6
7½		2·8	2·7	2·7	4·5
8½		2·8	2·5	2·6	4·6

Technique—*see* King, E. J. (1946) Micro-analysis in Medical Biochemistry, London, pp. 9–11. Colours read in Hilger absorptiometer.

As can be seen, some show a variation of as much as 0·8 mg. This variation does not appear to have any relationship to meals. I hope, in due course, to give fuller results. The plasma uric acid is calculated at the same time and it has a reading higher by 0·2–0·9 mg., but the curves of each patient are similar. Kersley and Gibson (1938) pointed out that the plasma uric acid and joint fluid uric acid had the same readings and the whole blood uric acid results on the same cases were lower. This work has been confirmed by many authorities and accepted: my results are an attempt to show that an isolated uric acid, unless grossly raised, is of little value. If the variation of 0·8 mg. is found constantly and the upper limit of 4 mg. is accepted as normal for whole blood, then gout cannot be diagnosed or suggested on the biochemical findings unless the whole blood uric acid is found to be 5 mg.%.

These investigations would suggest that a family in which the members have a high percentage of hyperuricæmia are more likely to react to stress by developing gout, but other psychosomatic disorders may commonly occur. I do not think that these investigations show that gouty families suffer unduly from "Adaptation Syndromes"; it is possible that they do but before arriving at that assumption cross references with family histories of peptic ulcers and asthmatics should be attempted.

Furthermore, I think that hyperuricæmia and stress are not the sole factors in an attack of gout; the term "stress" being used to cover both mental and physical trauma which may be induced by alcohol or other agents. It is probable that a vascular factor is also present. Finally, before an attack of gout occurs these three conditions at least must be fulfilled.

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Dr. Douglas H. Collins (Department of Pathology, The University of Leeds): *The Pathogenesis of Gout and Gouty Arthritis* [*Abridged*].

A consideration of the morbid anatomy of gout shows that the varying forms assumed by chronic gouty arthritis all result from uratic deposits in and around the joints and that the deposition of urates in the gouty individual provokes an inflammatory and cellular reaction. In the study of chronic gout, a distinction must be made between the urate deposits in avascular tissues such as hyaline and fibrous cartilage and in vascular tissues such as synovial membrane, bone-marrow and dermis. In avascular tissues there is neither inflammatory nor cellular reaction around the precipitated urates although such precipitation may lead to friability of the structure and its disintegration by mechanical forces. In this way urate deposits in articular cartilage can lead to early destruction of the cartilage and initiate the cycle of changes characteristic of osteo-arthritis. In the vascular tissues, an inflammatory response of greater or lesser severity occurs around the precipitated urates. This is followed by a cellular reaction and the growth of the characteristic "gout granuloma" comprising a central mass of urates, sometimes mixed with cholesterol or calcium, surrounded by a cellular zone of fibroblasts, histiocytes and foreign-body giant cells and by a capsule of collagenous fibrous tissue. This granuloma may be found in many situations and occurs in the bone ends at places where X-ray examination reveals punched-out erosions or osteolysis. Resorption of bone is effected by the reactive cellular tissue with or without the participation of osteoclastic giant cells. Resorption of bone ends, of the phalanges for example, may lead to subluxations and other deformities which are seen also in rheumatoid arthritis but result there from a different type of inflammation. Bony ankylosis occasionally follows the destruction of some small joints in gout.

The lesions of acute gout are not usually accessible for histological examination, but in acute gout we know that there is a focus of acute inflammation, generally centred in or near a joint, and that joint effusions aspirated towards the end of an acute attack contain great numbers of neutrophil leucocytes. Later in the course of the disease, tophaceous deposits are generally to be found at the site of earlier acute attacks. It has never been proved that each acute attack of gout is occasioned by a new deposition of urates in the tissues, but chronic manifestations of the disease most certainly are dependent upon this phenomenon.

New knowledge of the endocrine factors in gout and of the endocrine influences on various inflammatory processes arising from quite different causes leads us to reconsider the relation of the acute gout attack to urate precipitation. A state of depressed adrenocortical activity

might cause the tissues to react vigorously against changes in the physico-chemical state of the urates when these are present in the body fluids in a greater than normal concentration.

The inheritance of abnormalities of uric-acid metabolism has been described by American authors, and Dr. Wilson has given us what I believe to be the first report of the phenomenon in this country. Smyth, Stecher and Wolfson (1948) summarized the American work and, to Talbott's finding (1943) that about 25% of unaffected members of gouty families showed a symptomless hyperuricæmia, they added the information that abnormal plasma urate levels do not usually appear in males until after puberty and in females until just before, or just after, the menopause.

Forsham, Thorn, Prunty and Hills (1948) found that one of the most striking metabolic changes resulting from the injection of ACTH was a great increase in the urinary excretion of uric acid. Robinson, Conn, Block and Louis (1948) were the first to note differences in the effect of ACTH in gouty, as compared with normal, subjects. They postulated that the cyclic changes in urate, electrolyte and water secretion in gout, as well as many of the incidents known to provoke an acute attack, could be interpreted as manifestations of, or influences upon, adreno-cortical function. Relief of acute gout by ACTH injections is now well recognized and Boland (1950) has attained similar results with Cortisone. Evidence of abnormal endocrine constitution in gout has been fully reviewed by Wolfson (1950) who originally observed the abnormally small output of 17-ketosteroids in all gouty persons.

Had it not been for the classic demonstration by Hench, Kendall, Slocumb and Polley (1949) of the potency of adrenocortical hormone in rheumatoid arthritis and, later, in other diseases, it is possible that the earlier work on gout would never have achieved the significance it now commands. It is also possible that the hormonal effects observed in gout might have been attributed solely to the influence of these hormones on uric-acid metabolism. Salicylates cause a greater excretion of urates in the urine but benefit the clinical course of the disease far less than does ACTH. Research in other directions has now shown that Cortisone and ACTH powerfully influence certain types of pathological tissue reaction which are quite independent of any disturbance of uric-acid metabolism. The effects of these substances in gout, therefore, must be regarded as being twofold—upon the metabolism of uric acid and upon the tissue reactions which constitute the manifest disease.

A modern view of the pathogenesis of gout and gouty arthritis can be summarized as follows: Certain anomalies of uric-acid metabolism are inherited, one of which is hyperuricæmia manifest in males at an earlier age and to a greater degree than in females. Disturbances of pituitary-adrenocortical function occurring intermittently or permanently in individuals cause further variations in uric-acid metabolism and permit the development of the focal inflammations and systemic manifestations of acute gout. Before, during or after the acute gout attack deposition of urates occurs in the connective tissues, mainly in or around the joints. The progressive growth of uratic tophi together with the reactive or degenerative changes thereby induced in the tissues leads to the various types of change seen in the joints in chronic gouty arthritis.

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Dr. R. M. Mason (London): *Some Observations on the Blood Uric Acid Levels in Gout.*

Despite a voluminous and classical literature on gout, it has aptly been said that "the total impression produced by this literature is one of confusion rather than progress" (Folin, Berglund and Derick, 1924). Recent work by Hench *et al.* (1949, 1950) has provided a stimulus to new lines of thought and has thereby produced a large number of new observations. It is claimed that Cortisone or ACTH rapidly relieves the acute attack of gout and sometimes withdrawal precipitates a rebound attack, this phenomenon being accompanied by changes in urinary and blood uric acid values. This renders a review of blood uric acid levels necessary since one of the most important unexplained features of gout is the significance of the raised level. Somewhat arbitrary figures have been laid down as

representing the upper limits of normal; but there are so many provisos that these figures lose much of their value. It has been said that in gout the degree of hyperuricæmia fluctuates and the level may at times be normal, that not all cases of gout have hyperuricæmia, that the level rises just prior to an attack, that it falls just prior to an attack, or that it bears no relation at all to the acute attack; that hyperuricæmia may occur in many other conditions without the slightest suggestion of an acute paroxysm; that the intravenous administration of urate to a gouty subject will not precipitate an attack or that the local injection of uric acid into a joint will not precipitate an attack. Finally, colchicine which is generally agreed to be the only specific drug for this condition has no specific effect in lowering blood urate levels. Conversely, atophan which does cause excretion of urate is recognized as being quite ineffective in the acute stages.

Daily blood uric acid estimations were therefore made on a number of patients under standard conditions. 2 patients were observed during an acute attack. The first case (Fig. 1) was a man of 56 years of age who had had attacks of acute gout affecting the big toe since the age of 27. It can be seen that his blood uric acid was within normal limits on

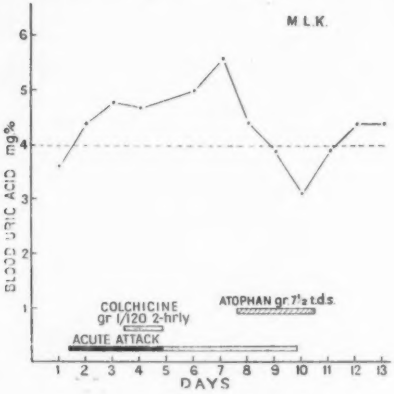

FIG. 1.

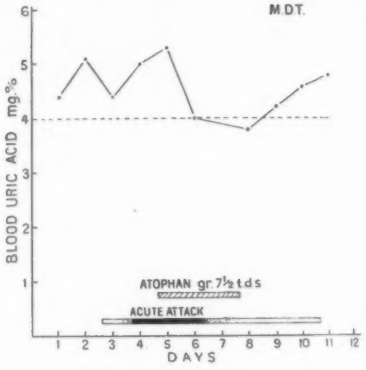

FIG. 2.

the day prior to his attack, rising during it and for two days after the acute phase had passed. Subsequently there was a fall to below previous levels as a result of the administration of atophan. The second case observed during an acute attack was a man of 57 who had had 56 acute attacks of gout (Fig. 2). Again there is no evidence of any striking change in the blood uric acid level before, during or after the attack. Atophan administration is again associated with a fall to normal levels. In neither of these two cases was there any suggestion of any specific changes in the blood uric acid levels in association with an acute attack of gout.

Fig. 3 illustrates the effect of one recommended form of interval therapy—that of fully colchicinizing the patient and following with tab. colchicin. grain 1/120 t.d.s. and, at the

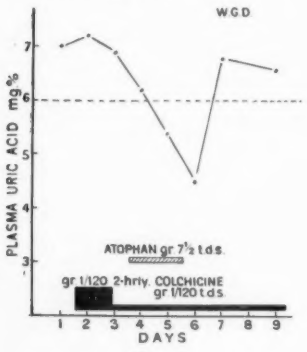

FIG. 3.

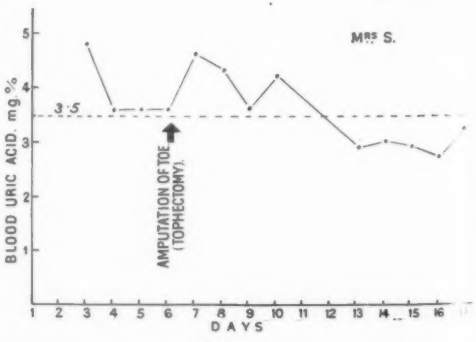

FIG. 4.

same time, administering atophan grains 7½ t.d.s. for two days. The graph shows the effect of such a regime on a man of 38 who had an extremely bad family history, both his father and mother being gouty subjects. It can be seen that the atophan is as effective in reducing the blood uric acid despite the administration of colchicine in full doses at the same time.

It has also been possible to observe the effects of surgery on the blood uric acid level of a gouty subject (Fig. 4). This patient was a woman of 47 years who had tophaceous deposits in the third toe of her left foot which became frequently infected and it was decided to amputate. It can be seen that her blood uric acid fell after admission, that there was a slight rise on the day following operation and it then fell to normal levels. No acute attack developed.

In these cases there has been no doubt of the diagnosis of gout: the clinical picture, the response to colchicine and the hyperuricæmia have been quite typical of the disease. However, there is frequently a considerable degree of doubt as to the diagnosis, especially as between gout and rheumatoid arthritis. There are many difficulties: it is well recognized that rheumatoid arthritis may, at least in the early stages, be episodic in character. Alternatively, gout may enter the chronic stage early. The radiological changes of gout, when present, may often be similar to those of rheumatoid arthritis and vice versa. Such episodic conditions as so-called palindromic rheumatism and intermittent hydrarthrosis are probably variants of rheumatoid arthritis. Thus the mere presence or absence of acute paroxysms of arthritis are not necessarily diagnostic. Finally, both rheumatoid arthritis and gout respond to ACTH and Cortisone and if this is the case, then these hormones will not provide a useful therapeutic test.

It seemed therefore that similar daily estimations of the blood uric acid might be helpful in distinguishing between these two conditions when single estimations might be misleading. In Figs. 1–4 there are at least two normal readings in each series; admittedly some of these were the results of treatment but it is known that salicylates such as aspirin have the effect of increasing excretion of uric acid and bringing down the blood level, and most patients with arthritis take aspirin. This procedure was followed therefore where the diagnosis was doubtful. Two examples illustrate the two sides of the picture: the first case was a man of 52 who had a six months' history of pain and swelling of the right big toe with an inflammatory reaction. He had later developed pain and stiffness of his hands. X-rays of his hands and feet were reported as showing "typical gouty deposits". His ESR was 80 mm. in the first hour (Westergren). The onset in the big toe and the radiological changes suggested gout and he had been diagnosed and treated as such. A single normal blood uric acid reading had been dismissed as insufficient to exclude the diagnosis. Serial blood uric acid readings, however (Fig. 5), showed a normal blood uric acid with a very flat,

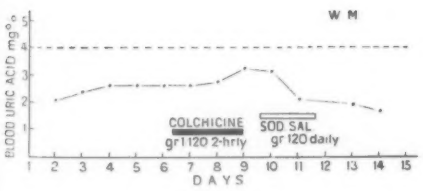

FIG. 5.

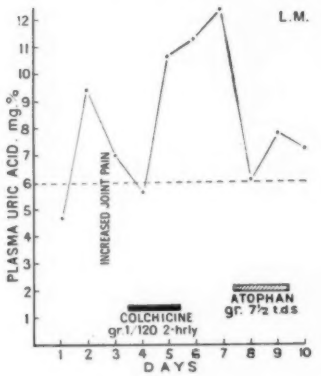

FIG. 6.

regular curve quite unlike those previously illustrated. He was given tab. colchicin. in full doses (grain 1/120 two-hourly for 20 doses) with the only result that he developed considerable gastro-intestinal disturbance and his blood uric acid level was raised to its highest recorded level of 3·2 mg.%. It seems probable that this rise was simply a reflection of his dehydration and perhaps this accounts for the rises seen in other cases. These findings would seem to exclude gout in this case.

The reverse picture is shown in Fig. 6. These readings were obtained from a man of 66

whose history was of a progressive polyarthritis of eight years' duration with remissions, his hands, shoulders and knees being mainly affected. There had been no constitutional disturbance and no loss of weight. The family history was negative for gout. X-rays of his hands showed marked periarticular porosis and his ESR was 68 mm. in the first hour (Westergren), the whole picture being suggestive of rheumatoid arthritis. Serial plasma uric acid readings leave no doubt as to the existence of a hyperuricæmia with a high fluctuating level.

It must be admitted that sometimes blood uric acid readings are as equivocal as the other diagnostic pointers in differentiating between rheumatoid arthritis and gout. There is thus a third type of case where the level of blood uric acid fluctuates around the upper limits of normal. Such were the findings in Case 7, a man of 40 who had had a polyarthritis for ten years beginning in his toes, spreading to his knees with a considerable effusion and slight flexion deformity. Within the last two years his hands and wrists had also become affected. Despite considerable pain and disability and apparently active disease, his ESR was only 12 mm. in the first hour (Westergren). He had had no relief from gold therapy. X-rays of his hands and feet were reported on as showing marked changes of gout but the appearances were consistent with rheumatoid arthritis. In this case therefore serial blood uric acid readings add little to the diagnosis.

Summary

If daily blood uric acid estimations are carried out, three types of curve may be obtained: (i) That of hyperuricæmia with a high fluctuating level; (ii) an irregular curve at around the upper limit of normal; and (iii) the normal curve with a low blood uric acid without marked fluctuation.

Conclusions

These very modest investigations make no pretence of being complete or conclusive. At the same time they suggest that in gout there are not always specific changes in the blood uric acid levels in association with an acute attack. They confirm as far as they go that it is not the concentration of uric acid in the blood that precipitates the acute attack and that some other factor is responsible, the nature of which is not yet understood.

Colchicine appears to have no specific effect on the blood uric acid levels whilst atophan has for a brief period. Finally, serial blood uric acid estimations may be of more value than isolated readings in establishing the diagnosis in some, but not all, cases.

Cases 4, 5, 6 and 7 were under the care of Dr. W. S. C. Copeman, to whom I am indebted for permission to publish.

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Section of Pædiatrics

President—KENNETH H. TALLERMAN, M.C., M.A., M.D., F.R.C.P.

[*November* 24, 1950]

Congenital Stenosis of the Trachea, and Other Congenital Abnormalities.—R. E. BONHAM-CARTER, F.R.C.P., and KEITH LOVEL, M.R.C.P.

Michael J., born 11.3.49, first attended in October 1949, under the care of Dr. Philip Evans, because of stridor since the age of 3 months and difficulty in feeding since he started solids at the age of 5 months. Normal pregnancy, normal labour. One week premature. Birth-weight 4 lb. 6 oz. Breast fed.

Family history.—Mother aged 35. Father 37. Both healthy. No consanguinity. Two other children, 7 years and 3 years, both well. No family history of anything similar.

On examination.—Mongol. Loud inspiratory and expiratory stridor, unaffected by position. Nil abnormal on palpation of neck. Chest—few scattered rhonchi. No cyanosis or clubbing. Otherwise N.A.D.

Investigations.—Barium swallow (Dr. J. M. W. Wells): "The œsophagus is displaced to the left and kinked forward and narrowed at the level of the aortic arch. The heart outline and great vessels are otherwise normal. The appearances are those of an anomaly of the great vessels, probably a vascular ring."

10.1.50: Angiocardiography attempted, but abandoned owing to laryngeal spasm on induction of anæsthesia.

19.9.50: Bronchoscopy (Professor R. S. Pilcher): "A narrowing of the trachea at the level of the thoracic inlet. No anterior pulsation was seen and I was convinced that the tracheal narrowing was intrinsic."

22.9.50: Tracheogram: Forward displacement and narrowing of the trachea at the thoracic inlet (Fig. 1).

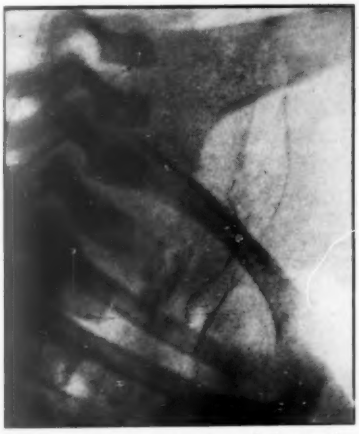

FIG. 1.—Lateral tracheogram, showing narrowing of the trachea at the thoracic inlet.

Progress.—The difficulty in feeding has become much less, and he can now swallow most solids, but the stridor persists. He crawls and stands but does not yet walk.

Comment.—The barium studies showed œsophageal compression by an anomaly of the aortic arch, and it was at first thought that the stridor might be due to compression of the trachea by the same cause. However, bronchoscopy showed narrowing of the trachea at the root of the neck, where nothing pressing on the trachea could be palpated, and the tracheal stenosis must therefore be a separate congenital abnormality.

The gravity of the condition, and the possibilities of treating it by resection of the affected segment or by dilatation with bougies were discussed. No operative treatment was felt to be indicated for the vascular abnormality, since the dysphagia, which was at first a severe symptom, has been gradually getting less.

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Polyostotic Fibrous Dysplasia.—CLIVE UPJOHN, M.D., M.R.C.P., D.C.H.

Patricia G., aged 3. (1) Progressive cystic condition of the bones. (2) Abdominal skin lesion. (3) Recurrent hæmothorax.

History.—At 2½ years admitted to hospital for fracture of ribs, right side of chest, from a fall. No other abnormality, apart from abnormal area of skin across right side of abdomen. X-ray of chest showed fractured ribs, and also multiple small cysts in the ribs and larger cysts in the upper ends of both humeri. X-ray of the skeleton showed other cysts in the pelvis and upper end of femora (*see* Fig. 1).

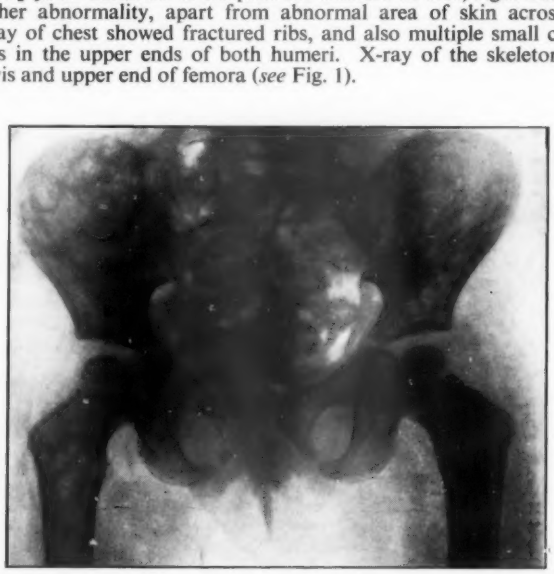

FIG. 1.—X-ray showing many cystic spaces in bones of pelvis and upper end of femora.

Blood calcium 10·7 mg.%. Blood inorganic phosphorus 5·7 mg.%. Serum alkaline phosphatase 19·1 units (King-Armstrong). Blood count normal. Blood cholesterol 175 mg.%. Blood W.R. and Kahn negative. Urine N.A.D.

Tibial bone-marrow: Nucleated marrow cells normal but unusually dilated with blood. No abnormal cells seen. Compatible with marrow replacement by fibrovascular tissue. Biopsy of rib: The cancellous bone shows spaces of varying sizes; the large ones appear quite empty with scanty marrow plastered against the walls and the smaller spaces show serous fluid. No other significant changes.

Discharged from hospital after six weeks without definite diagnosis. In good general condition. She was seen intermittently as an outpatient and her condition remained unchanged.

Re-admitted 11.10.50 after another fall on her chest, fracturing some left ribs.

On admission.—Moderately distressed with rapid respirations. X-ray: Bilateral pleural effusion. Paracentesis: Deeply blood-stained fluid.

During the past six weeks the bilateral blood-stained pleural effusion has required repeated aspiration of up to 20 oz. at a time. X-rays of the skeleton show increase of the cystic bone condition.

Blood chemistry unchanged. Bleeding and clotting times normal. Platelets normal. Mantoux 1/1,000 negative.

Skin lesion has been described by Dr. Prosser Thomas as suggestive of pseudoxanthoma elasticum.

Skin biopsy (Dr. I. W. Whimster): The lesion appears to be due to some fault in the structure of the connective tissue of the skin, and is in some respects similar to the condition known as pseudoxanthoma elasticum.

Discussion.—Primary hyperparathyroidism was excluded in view of the normal blood chemistry, absence of general symptoms and the absence of generalized decalcification in the X-ray appearances of the bones. Multiple myeloma was considered but has not been recorded in childhood; no Bence Jones protein was present in this patient's urine. Generalized xanthomatosis of bone was excluded by the biopsy of the bone and bone-marrow examination. The distribution of the cysts in the bones was not that found in

sarcoidosis; the child did not present any other feature associated with this condition and the skin condition was not like that sometimes occurring in sarcoidosis.

It was submitted that the diagnosis in the case was polyostotic fibrous dysplasia.

Uehlinger (1940) collected a number of cases and described the clinical picture; according to his analysis the essential features are:

(1) Lesion of bone developing in the marrow spaces and consisting essentially of a fibrous dysplasia.

(2) The lesion may involve several or many bones and be unilateral or bilateral, though not symmetrical.

(3) Special predilection for long bones and neighbouring shoulder and pelvic girdles. Proximal bones are more extensively affected than distal bones, the femur appears to be invariably involved.

(4) The disease affects primarily the diaphysis. Joints and epiphyses remain unaffected except in rare instances after the epiphyses and metaphyses have become united.

(5) The serum calcium and inorganic phosphorus levels are normal—the phosphatase normal or slightly raised.

(6) The disease condition is a disease of childhood and becomes stationary in adult life.

Reference was also made to Falconer and Cope's (1942) review of the literature on Albright's disease.

These authors maintained that the bony changes in Albright's syndrome were identical with those in polyostotic fibrous dysplasia, and that the only difference was the presence of pigmentation of the skin (due to melanin deposits) and endocrine disturbances, typically precocious puberty.

It was submitted that this patient fulfils all the criteria for polyostotic fibrous dysplasia, but the nature of the skin lesion is not that associated with Albright's syndrome.

The skin lesion has been described by Dr. Prosser Thomas as that due to pseudoxanthoma elasticum, not usually associated with this syndrome, but could presumably occur independently as a separate congenital abnormality.

The views of the meeting were asked for but no alternative diagnosis was suggested.

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Translucent Milk Incisors.—J. M. D. Hooper, B.M. (for R. C. Mac Keith, D.M.).

Raymond T., born 23.8.46.

Pregnancy normal. Birth-weight 8 lb. Breast fed 8 months and had cod-liver oil. Dentition and other milestones normal.

In the family history one cousin had similar milk teeth but the permanent dentition is normal.

At age 3½ years when seen for minor respiratory ailment he was noticed to have translucent milk teeth. The structure of the teeth appears normal.

Coarctation of the Aorta with Congenital Œdema of the Feet.—O. D. Fisher, M.R.C.P. (for W. G. Wyllie, F.R.C.P.).

John M., aged 8 months.

History.—Persistent though slightly variable swelling of both feet present since birth.

On examination.—Weight 17½ lb. C.V.S. Systolic murmur to the left of the sternum and at the angle of the left scapula posteriorly. Blood pressure right arm 135/80, left arm 130/70, left and right leg not recordable. Femoral pulsations were not felt and could not be recorded with oscillometer. Pitting œdema present on the dorsum of feet.

Investigations.—R.B.C. 4,300,000; Hb 89%; W.B.C. 8,600, lymphocytes 71%. 8.5.50: Blood urea 29 mg.%. Urine normal. E.C.G.: Left axis deviation.

X-ray chest: Abnormal superior mediastinal shadow. Screening: Superior mediastinal shadow probably thymus. Heart size upper limit of normal. Aortic knuckle not well seen. Pulmonary conus, pulmonary artery, pulmonary vascular markings normal. Barium swallow: No good vascular impression, normal cardiac impression.

15.11.50: Blood urea 39 mg.%. Serum cholesterol 140 mg.%. Serum proteins: Albumin 3·2 grammes %, globulin 3·1 grammes %, total 6·3 grammes %. W.R. negative.

Generalized Retardation, with Renal Impairment, Hypercalcæmia and Osteosclerosis of Skull.—N. R. BUTLER, M.D., M.R.C.P. (for BERNARD SCHLESINGER, M.D., F.R.C.P.).

John S., born 4.12.48, aged 2 years.

History.—Fourth child. No family history of congenital osseous or renal disease. Birth weight 6¾ lb. Pyloric stenosis at 6 weeks treated surgically. Never thrived normally in spite of normal diet and vitamin intake. Always anorexia and constipation with delayed mental, physical and skeletal development. Raised head at 6 months, sat up at 18 months, now at 2 years cannot walk or take normal interest in surroundings. Always had harsh apical systolic murmur without cyanosis or cardiac enlargement, probably ventricular septal defect. Never had polyuria or polydipsia. First carpal ossific centre appeared late, at 18 months. Renal and osseous lesions first discovered at 21 months.

On examination.—Dwarfed, wasted, hypotonic child, with physical development of approximately 9 months and mental development approximately 1 year. Height 27½ in. Weight 27 lb. Odd facies with epicanthic folds, receding mandible and low set ears, not that of a mongol or a cretin. Anterior fontanelle widely patent. High arched palate. Alternating convergent strabismus. Loud precordial systolic murmur without thrill. Generalized lack of subcutaneous tissue. All reflexes just present.

Investigations.—Blood count: R.B.C. 4,160,000; Hb 88%; W.B.C. 14,500 (4% myelocytes on 1 occasion). E.S.R. 23 mm. in one hour (100 mm. tube). Urine: Albumin a trace. Sugar

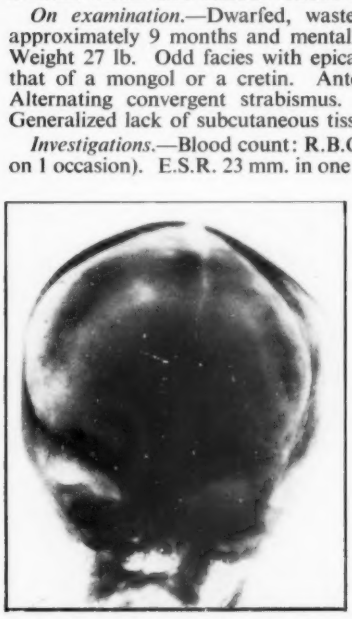

FIG. 1.—A.P. view of skull showing sclerosis of base and frontal bones.

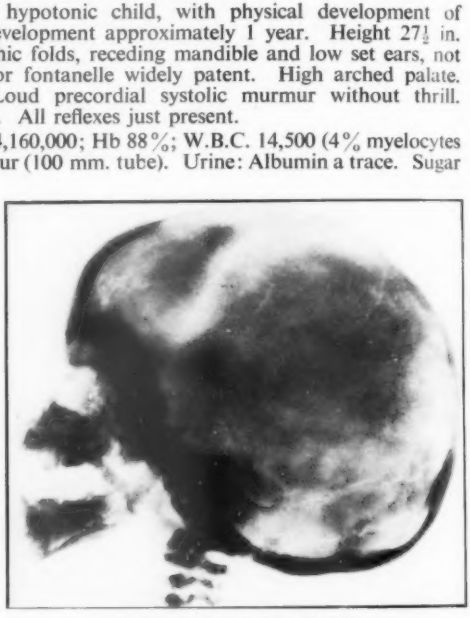

FIG. 2.—Lateral view of skull.

nil. Deposit 5–10 W.B.C. per high power field. Culture (twice) scanty growth of *B. coli*. Specific gravity test failed to concentrate urine above 1,010.

Urea clearance: First hour 37·6% (standard clearance); second hour 23·6% (standard clearance).

Blood chemistry (Dr. W. W. Payne).—Serum calcium 13·4 mg.%, blood inorganic phosphorus 5·0 mg.%, serum alkaline phosphatase 13·6 K.A. units, blood cholesterol 269 mg.%.

X-ray report.—Frontal bone and base of skull (Figs. 1 and 2) show considerable increase in density with some actual thickening of bone structure. Long bones show dense transverse lines in the metaphyses, probably representing a disturbance of bone formation in the first year of life. Bone age one year.

X-ray of renal tract: No evidence of calcification. X-ray of soft tissues: No evidence of calcification. Cystoscopy (Mr. Twistington Higgins): Bladder normal. Ureteric orifices normal. Retrograde pyelogram impossible as ureteric catheters could only be introduced for a short distance.

Comment.—The main interest lies in the cause of the sclerosis of the base of the skull, here associated with dwarfism, congenital heart disease, renal impairment and hypercalcæmia. Such X-ray changes have been recorded in Albers-Schönberg disease, fibrous dysplasia of bone, phosphorus and fluoride poisoning, extreme hypoparathyroidism and the rare Pagetoid type of hyperparathyroidism.

Albers-Schönberg disease is essentially a generalized affection of the whole skeleton, with a brittleness, hardness and lack of moulding of bone, with a tendency to spontaneous

fractures, cranial nerve palsies, including blindness and deafness, and later a leuko-erythroblastic anæmia. Flood (1929) recorded one case with hypercalcæmia of 16·2 mg.% and since then many authors have incriminated hyperparathyroidism as a possible cause, firstly on the autopsy finding of a parathyroid adenoma in a case of osteosclerosis by Péhu (1931), secondly on the experimental evidence of Selye (1932) who produced osteosclerosis with repeated injections of parathormone in rats, and finally on the histological evidence of areas of rarefaction alternating with the sclerotic areas in the affected bony metaphyses.

It would be tempting to postulate hyperparathyroidism in the present case, especially as Albright (1948) has described several cases of hyperparathyroidism with so-called Pagetoid osteosclerosis, due presumably to a positive calcium balance resulting from a high calcium intake such as occurs in infancy. The renal lesions could be either unconnected or secondary to hypercalcæmia even in the absence of renal calcification on X-ray, or alternatively could be the primary cause of a renal osteodystrophy with secondary hyperparathyroidism. The latter is unlikely in view of the absence of acidosis and advanced uræmia. Another possibility here is an abnormal sensitivity to a slightly increased calcium intake, which according to Anderson and Schlesinger (1942) may in the presence of renal damage cause osteosclerosis and even metastatic calcification.

POSTSCRIPT.—Later metabolic studies in this case have shown that following injection of parathormone there is a normal rise in serum calcium and urinary phosphate excretion, with a fall in blood organic phosphate. There is also strongly positive calcium and phosphorus balance with retention of nine-tenths of ingested calcium and half of ingested phosphorus.

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Ferrous Sulphate Poisoning.—N. F. ELLIOTT BURROWS, B.M. (for NORMAN HILL, M.D.) T. W., aged 14 months.

Admitted to Belgrave Children's Hospital at 1.30 p.m. 7.11.50, with a history of having swallowed many $FeSO_4$ tablets one hour previously. Ten minutes later he had the first of a series of vomits, which produced no tablets, but only green-tinged fluid.

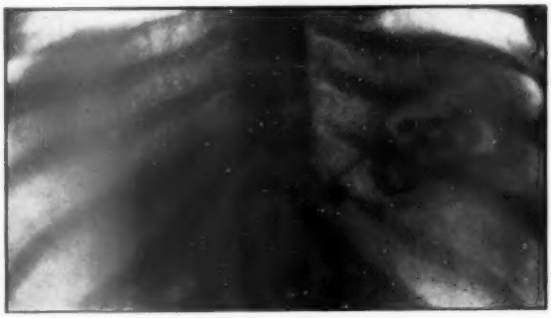

FIG. 1.—Ferrous sulphate tablets in stomach.

An immediate X-ray revealed what appeared to be 16 tablets in the stomach, and 3 or 4 others which had left it (Fig. 1).

The child was induced to vomit again by mechanical means, but no tablets were forthcoming. Vigorous washing out of the stomach was then undertaken with a total of 3–4 pints of sterile water. A brown liquid was obtained which gave a positive guaiacum test.

The child's condition gradually deteriorated, and by 3 p.m. he was extremely shocked—pale, cold, clammy and comatose, with subnormal temperature, rapid thready pulse and rapid shallow respirations.

At 5 p.m. his condition had improved slightly and he passed a large black stool, which also gave a positive guaiacum reaction. By 7 p.m. he was not so well and becoming drowsy again. As the CO_2 combining power of his blood was only 42 vols.% he was given 0·75 gramme sod. bicarbonate hourly for five hours. By 10.30 p.m. he was markedly better, both pulse and respirations were almost normal, and although he passed 3 black stools during the next five days, he never gave any further anxiety.

His CO_2 combining power was 54·8 vols.% on the morning of 9.11.50.

Sickle-cell Anæmia.—P. M. M. PRITCHARD, M.B. (for R. E. BONHAM-CARTER, F.R.C.P.).

A white boy aged 12. Attacks of backache with pyrexia for four years; pale for one and a half years. Jaundiced since May 1950. Admitted June 19, 1950. Liver 4 cm. below right costal margin. Spleen not felt. Heart enlarged. Neck veins engorged.

Investigations.—Hæmoglobin 54%. Numerous sickle cells. Reticulocytes 19%. Osmotic resistance of R.B.C. increased. Excess of urobilinogen in urine. Empirical liver function tests strongly positive. Plasma alkaline phosphatase 14 K.A. units. Indirect van den Bergh 4·8 units. Serum proteins: Albumin 4·3%; Globulin 3·4%. Coombs' Direct and Indirect tests negative. W.R. negative. E.S.R. 52 mm. in one hour (Wintrobe). X-ray of skull showed thickening and coarse mottling of calvarium. Chest X-ray showed slight cardiac enlargement.

Progress.—On July 11, 1950, he had an "abdominal crisis" with diarrhœa, then constipation with gross abdominal distension and backache. Jaundice increased (5·6 units). Attack subsided in four days.

On July 15, 1950, he had acute pulmonary embolism with congestive cardiac failure. Hæmoglobin 40%. He was transfused with packed cells from 2 pints, and gradually improved until discharge on August 9, 1950. Has kept well since and hæmoglobin remained over 50%, though heart is still enlarged, and chest X-ray shows bilateral opacities.

Family.—Father: English, killed eleven years ago. No relatives available. Mother: English; her grandfather married a Barbadoan. Mother and grandmother show sickling in wet preparation, and are not anæmic.

Comment.—A clear case of sickle-cell anæmia in a white boy. The mother and maternal grandmother show the trait, and there is a coloured maternal great grandmother.

Interest has been aroused in this disease by the recent work of Pauling (1949, 1950), and Perutz and Mitchison (1950). The former showed by electrophoretic studies that there was an abnormal hæmoglobin in sickle-cell anæmia. In "trait" individuals the abnormal hæmoglobin was present in a variable proportion between 25 and 44%. The latter authors have demonstrated that sickle cells behave like crystals of hæmoglobin under polarized light, whereas unsickled cells and normal red cells do not. The solubility of reduced "sickle" hæmoglobin in phosphate buffer was found to be less than one-hundredth that of oxy-"sickle" hæmoglobin and normal hæmoglobin.

The hypothesis that sickle cells contain hæmoglobin in the crystalline state would help to explain the mechanism of sickling, and the consequent capillary embolism which is characteristic of the disease. The remittent course with acute crises is so far unexplained.

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Hypochromic Anæmia with Bone Changes in the Skull.—BERNARD LAURANCE, M.R.C.P., D.C.H. (for WILFRID SHELDON, M.D.).

Kathleen P., aged 8 months, was the fourth child of a healthy family. Her deceased maternal grandmother was said to have been dark and often mistaken for an Oriental, but no confirmation of this was possible. The father was British. Neither parent had resided abroad. There was no consanguinity.

After a normal pregnancy, the patient was born by a rapid vertex delivery at full term. Birth-weight 7 lb. 6 oz. She was breast fed for 2 months and then put on a brand of full cream powdered milk. Cod-liver oil and orange juice had been given in adequate amounts since the age of 1 month.

On 26.5.50, aged 2½ months, she was noticed to be pale and sallow at the post-natal clinic. The hæmoglobin was 40% (5·9 grammes). R.B.C. 3,600,000 per c.mm. C.I. 0·56. She was treated with ferrous sulphate 3 grains daily.

On 8.6.50 she was admitted. Weight 11 lb. 9 oz. She was a pale, waxy-looking baby without clinical jaundice. The stools were normal. The spleen was enlarged to the umbilicus

and firm. The liver was slightly enlarged and firm. No abnormality was found in any other system. The following investigations were carried out: Blood group A. Rh-positive. Direct Coombs' test negative. Hb 20% (3 grammes). R.B.C. 2,600,000 per c.mm. C.I. 0·38. Hæmatocrit 12%. M.C.V. 46 c.μ. Reticulocytes 0·1% (on several occasions). W.B.C. 7,200 per c.mm. (neutrophils 57·5%, eosinos. 3%, basos. 0·5%, lymphos. 30%, monos. 9%). 618 nucleated R.B.C. per c.mm. Platelets "normal". Red cells very pale, but a few well hæmoglobinized.

30.6.50: Tibial marrow: Hyperplastic active marrow with ample deposits of iron and nodules of primitive red cells, but lack of late erythropoiesis.

12.6.50: Urine: No R.B.C., urobilinogen or urobilin. Stools: occult blood weakly positive on numerous occasions. No pathogens, cysts or ova. T.B. jelly negative. Red cell fragility normal. 6.10.50: Bleeding time 3 min. Prothrombin time 17 sec. (normal 12). 11.10.50: Fæcal stercobilin excretion within normal limits. W.R. negative. 19.10.50: Gastric residues: Free HCl nil. Total acid 4 mEq/lit. 24.10.50: Serum Ca 9·5 mg./100 ml. Plasma inorganic phosphorus 5·9 mg./100 ml. Serum phosphatase (alkaline) 54·7 K.A. units per 100 ml. (normal 3·7 to 13·1). 25.10.50: Eight-day fat balance: Average absorption 97·6%. 26.10.50: Serum iron 244 μg./100 c.c. (normal for children 0·60 μg.—Valquist.)

X-rays: 15.6.50: Long bones and skull normal. 15.8.50: Skull and wrists normal. 10.10.50: Some osteoporosis and reduplication of cortex in shafts of some long bones; thickening of frontal and to a lesser extent of parietal bones of skull resembling changes seen in Cooley's anæmia. Barium swallow, follow-through and enema normal.

Progress and treatment.—Seven blood transfusions were given between June 8 and November 20 (approximately five months) at two- to six-week intervals. The hæmoglobin was raised each time to between 60 and 70% and fell again to between 30 and 45%. At first the splenomegaly was reduced by each transfusion. More recently the spleen has remained small. Iron and ammonium citrate, colliron, copper, hepatex, ascorbic acid and vitamin B_{12} have all been given without apparent benefit. The flattening and marked bossing of the skull have appeared in the last two months.

Discussion.—Because of the fall in hæmoglobin despite iron therapy, the blood film showing anisocytosis, poikilocytosis and a few target cells, and the marrow film showing hypoplasia of the erythropoietic tissue with a normal white cell series, a diagnosis of congenital hypoplastic anæmia was considered most likely. Leukæmia was a possibility.

However, further marrow smears revealed a hyperplastic marrow with ample iron deposits.

Further points requiring explanation were the persistently positive occult bloods, the frequency of blood transfusions required despite lack of evidence of hæmolysis, and the remarkable changes in the skull similar to those seen in Cooley's anæmia. Two possibilities remain as to the cause of this anæmia:

(1) Blood loss with or without the ability to utilize the adequate iron deposits in the marrow.

(2) There is an abnormality of erythropoiesis and/or hæmoglobin synthesis allied to the Cooley type of anæmia.

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Craniosynostosis.—BERNARD LAURANCE, M.R.C.P., D.C.H. (for WILFRID SHELDON, M.D.).

Gloria K. aged 2 years and 2 months, was the second of three children. Her family was healthy with no known skeletal deformities.

The mother fell when 3 months pregnant, but otherwise pregnancy had been normal. Delivery was at full term. Birth-weight 9 lb. 3 oz. Breast fed three months. Milestones were only a little backward: Sat up at 11 to 12 months; walked at 20 months; talking commenced at 16 months. Aged 7 months, she had whooping cough.

On 17.9.49, aged 1 year, she was admitted to hospital as she was underweight and development was retarded. There was some proptosis, more on the right than left, and the ears stood out prominently. Skull circumference was 18 inches. The anterior fontanelle had irregular edges and was elevated above the rest of the skull. Seborrhœic dermatitis was present.

Skull X-ray: "Fontanelle wide and patent; increase in convolutional markings, and some of the sutures are not visible." She was discharged on 28.9.49 with a diagnosis of mental backwardness.

In the last six months, the eyes had become more bulging, a right squint had developed and the anterior fontanelle had become more prominent.

She was readmitted on 30.8.50, pale, able to walk, and with an indistinct voice. Proptosis marked and nose rather beaked. Fontanelle bulging. Head circumference 18½ inches. No other skeletal or other abnormality (Fig. 1).

In the eyes, there was weakness of the internal recti, myopia, and no papillœdema. The

right was almost blind. X-ray of skull: "Bones surrounding anterior fontanelle pushed outwards and everted as if the brain is herniating through. Marked convolutional markings, with closure of all except the sagittal and occipito-sphenoidal sutures."

Progress.—7.9.50: Adenoidectomy.

17.10.50: Craniotomy (1st stage) by Mr. Wylie McKissock. 1 cm. width of bone excised in the line of the coronal sutures and tantalum foil inserted.

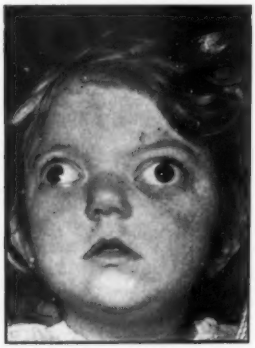

FIG. 1.—General facial appearance before operation showing proptosis and beaked nose.

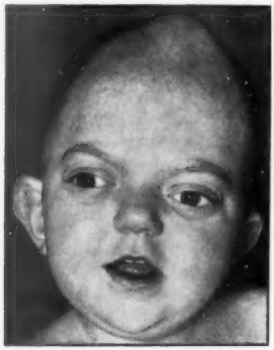

FIG. 2.—Appearance soon after operation showing elevated anterior fontanelle. The proptosis has lessened.

7.11.50: Craniotomy (2nd stage) by Mr. Wylie McKissock. 1 cm. width of bone excised from inion forwards to join the first incision, and tantalum foil inserted.

Both wounds healed satisfactorily, and the child appeared mentally to have progressed well. The proptosis had lessened (Fig. 2).

I wish to thank Mr. Wylie McKissock for permission to publish details of this case.

Discussion.—Although this might be called Crouzon's disease (1912) there was an absence of some of the features originally described, viz. small maxilla and absent sinuses, prognathism and a familial or hereditary history. In any case, the division of this and other similar skull deformities into definite entities appeared incomplete.

As to causation there appeared to be three theories:

(1) An error in the development of the mesenchymal capsule in which the cranium is formed, the size of the cranial bones being reduced and the sutures being hypersusceptible to premature ossification (Park and Powers, 1920).

(2) There are ectopic centres of ossification in the membranous tissues of the sutures causing premature closure.

(3) Where the skull bones touch they fuse (Greig, 1926).

Craniotomy originated probably by Lane (1892) had fallen into disrepute as he operated on many microcephalics. The operation might also fail to relieve ocular defects if the optic foramina were narrowed (Wilson, 1940).

Park and Powers (1920), Faber and Towne (1927, 1943), and Woodhull (1942) advised craniotomy in early life and claimed that apart from mild brachycephaly their patients showed no proptosis or visual defect and had high grade intellects. King (1938) recommended morcellement.

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Section of Otology

President—D. F. A. Neilson, F.R.C.S.

[*November* 3, 1950]

The Vulnerability of the Eustachian Tube

PRESIDENT'S ADDRESS

By D. F. A. Neilson, F.R.C.S.

In this Address it is my purpose to introduce for discussion certain problems at once controversial and of everyday practical importance.

It is proposed to consider: Firstly, the pathological factors, in particular infections, which damage the eustachian tube and so impair its function.

Secondly, the anatomical and other factors which enable it to resist such injury.

Finally, the surgical and other methods of treatment.

The essential function of the tube is the equalization of air pressure on the two sides of the tympanic membrane. Much discussion and thought has been devoted to the mechanical factors, including the action of the tubal muscles which regulate the opening and closing of the tube.

The facts appear to be that the cartilaginous portion of the tube has the characteristics of a soft rubber tube, with the edges of the orifices smoothly rounded off and held in apposition by light pressure from without. By the muscular action of swallowing the nasopharyngeal entrance to the tube can be opened, as occasion requires, to let air in or out, and then at once returns to its state of passive closure. The structure of the lining membrane of the tube at its nasopharyngeal end is uncomplicated, consisting of ciliated epithelium on a base of connective tissue, with a fair amount of glandular and lymphoid tissue.

Pathological Factors Affecting the Eustachian Tube

(1) *Occupation.*—Two occupational disorders need consideration, both of which involve rapid increases of barometric pressure: Aviation and Caisson work.

Aviation.—Descent from a height may involve increase of barometric pressure amounting to 100 mm. Hg. or more. If this takes place rapidly, without the subject's being aware of its occurrence and having the opportunity of maintaining the patency of his tube by swallowing, a severe lowering of intratympanic pressure in relation to that of the atmosphere may occur with pain, deafness and retraction of the tympanic membrane. It may be found impossible to correct this by opening the tube by swallowing. In subjects whose tubal patency is impaired by catarrhal conditions, flying should not be encouraged. If it is necessary, then they should be carefully advised to maintain the patency of their tubes during descent by the use of nasal inhalations during the flight, by sucking sweets and by the timely application of Valsalva's procedure.

Caisson work.—Similar conditions of eustachian blockage may occur with the raising of atmospheric pressure which occurs in a caisson. Less has been heard of this problem by otologists than of the closely allied problem in aviators—possibly

because caisson workers are a much smaller group, and are probably more expert in maintaining their tubal patency. Furthermore, the condition, if it occurs, can be relieved by decompression to normal ground pressure. In aviators a comparable manœuvre, that is to say a prompt re-ascent to 10,000 ft., cannot be so easily arranged. On the whole it seems true to say that passengers in air liners are not as well instructed as they might be in carrying out the necessary simple precautions against eustachian blockage.

(2) *Infection.*—Infective processes in the nasopharnyx affect the working of the tube in two ways. Firstly they impair the efficiency of its opening mechanism in the face of inequalities of barometric pressure on the two sides of the tympanic membrane. Secondly, they lead to infection of the tympanum by way of the tube. Predisposition to this kind of tympanic infection varies with age, and appears also to exhibit well-marked familial incidence. It must be in the experience of many otologists to encounter the tendency to recurrent otitis media in several members of the same family. Such cases usually clear up after puberty.

Treatment

A very large part of the work of the otolaryngologist is devoted to the surgical and other treatment of nasopharyngeal infection with enlarged and infected adenoids, leading in many cases to recurrent acute or subacute otitis media.

This work is of the utmost importance, and the technique of its effective performance would seem deserving of the most careful consideration.

The two main methods are: (1) Surgery; (2) Irradiation.

(1) *Surgery.*—Whether irradiation of nasopharyngeal lymphoid tissue should ever be necessary following a properly executed surgical removal of lymphoid tissue in the nasopharynx can perhaps be questioned. It is probably correct to advise that in no case should consideration be given to irradiation until surgery has been tried. It may be added that the number of patients requiring irradiation after adenoidectomy is in indirect proportion to the efficiency with which this operation is carried out. It is, therefore, important that the surgical efficiency of the procedure should be maintained at as high a level as possible.

For the last twenty years I have, in all my tonsil and adenoid operations, practised the removal of the adenoids as a first step. Thereafter I have always carried out a very careful palpation of the nasopharynx to ensure complete removal. This is followed by visual examination of the lower edge of the adenoidectomy wound. Adenoidectomy carried out in this way can be done deliberately and accurately. This is not the case if it is carried out, as is usual, at the end of the operation, when the child is entering a stage of light anæsthesia and when contractions of the palatal muscles render it difficult and may introduce a risk of damage to the superior constrictor muscle.

For the operation I have always used a curette, and have never found evidence of permanent damage to the lining mucosa of the nasopharynx, with resultant nasopharyngeal scarring and catarrh. The curette must be sharp and the cutting sweep confined to the roof and posterior wall of the cavity.

Claims have been made that the adenotome is a more scientific type of instrument than the curette. In my experience, however, it often fails to remove the adenoid tissue at the sides of the roof of the nasopharynx and even in the roof itself. For this reason it is not possible with an adenotome to effect anything but the partial removal of the adenoids.

Following the removal of the adenoids I have always inserted a firm plug in the nasopharynx to arrest the hæmorrhage whilst the tonsillectomy is being carried out. I used, at one time, to think that the insertion of this plug might increase the liability to infection of the eustachian tube, but it certainly does not do so any more than any other method.

(2) *Irradiation.*—This is best reserved for the elimination of swollen and degenerate lymphoid tissue on the lateral wall of the nasopharynx. It is, of course, necessary to stress that in the carrying out of this treatment it is essential to have the guidance of a competent radiotherapist. The dangers of overdosage have been stressed and are familiar to us all, in particular damage to the pituitary. On the other hand the intrinsic susceptibility to irradiation of lymphoid tissue is so much greater than that of other structures in the neighbourhood as to make it unlikely that any serious damage to this would occur, in particular if the treatment is carried out under the guidance of a radiotherapist.

In support of this opinion may be quoted the absence of damage to the pituitary in numbers of patients successfully treated by deep X-ray or teleradium therapy for malignant disease of the upper nasopharynx, the lateral walls of the nasopharynx and the soft palate, even though in such cases very heavy irradiation is used.

Other Forms of Treatment of Nasopharyngeal Infection and Tubal Inefficiency

Treatment of chronic infection and enlargement of the adenoids may also be carried out by breathing exercises, nasal instillations, positional drainage, &c., as practised in various clinics. No description of the treatment would, however, be complete without reference to the use of plain steam inhalations, which I have found of the greatest use in many cases of acute infection of the nose and nasopharynx.

Mention must finally be made of the place of the eustachian catheter in the treatment of tubal inefficiency.

In these cases it is my experience that the only kind of inflation that commonly does any good is that which can be induced by auto-inflation or politzerization. This is best used during a period of subacute nasopharyngeal congestion. In chronic cases, the catheter may be used, but my successes here are very, very few.

When fluid is present in the middle ear as a result of temporary tubal closure, I resort to incision of the drumhead and aspiration through the meatus rather than employ suction or inflation through the eustachian catheter.

I have never had a case in which the tympanic membrane failed to heal completely after it had been incised for this purpose.

Mr. V. E. Negus referred to some recent investigations by Hilding, who had shown that a plug of mucus occluding the lumen of the trachea or a bronchus could be driven along it by ciliary action with a force capable of causing collapse of the related area of lung. Removal of the plug caused re-inflation of the lung.

It was suggested that ciliary action in the eustachian tube might in the same way bring about reduction of pressure in the tympanic cavity with retraction of the membrane. This seemed to provide a better explanation of the reduction of tympanic pressure which followed eustachian obstruction than that usually offered, namely, the absorption of oxygen from the imprisoned tympanic air. Mr. Negus suggested that the validity of this explanation might be tested by gas analysis of the tympanic air in cases of eustachian obstruction.

When operating for adenoids he had always been nervous of producing scarring in the naso-pharynx, which would prevent regeneration of the ciliated epithelium and so lead to post-nasal catarrh. For this reason he had for many years avoided the use of curettes. He preferred to displace the mass of adenoids towards the mid-line with the finger. Thereafter it was possible with one or two applications of an adenotome of the right shape to remove the lymphoid tissue completely.

Mr. H. S. Kander said that there was a large number of children to-day who had had tonsils and adenoids removed and yet had recurrent otitic attacks or persistent deafness. He thought they should be dealt with first by surgical treatment of any recurrent adenoids, but there was still a residual number of children who did not respond. It had been found in his Department in these cases that the results of deep X-ray therapy had been excellent. Radon applicators in his personal opinion were very difficult for small children unless an anæsthetic was given; the dosage, too, cannot be controlled properly. With deep X-ray therapy symptomatic improvement of deafness was obtained, according to statements by the mothers and teachers in about 90% of cases, while 78% showed definite measurable improvement by audiometer—in some of them the improvement being over 20 decibels. There were no ill-effects, but in 2 cases slight attacks of transient parotitis followed the treatment.

Professor Paul Frenckner (Stockholm) said that one of the things which had interested him in the President's Address was the technique of dealing with lymphoid tissue. He could not agree with Mr. Negus on this point. He was not afraid to remove the lymphoid tissue and he believed it was important to remove it as completely as possible. If there was adenoid tissue just behind the posterior lip of the eustachian cushion it would press this forward and close the mouth of the tube. It was useful to remove it and leave room for the posterior lip to expand backwards, so opening the tube.

With regard to the value of radiotherapy, with lymphoid tissue in the fossa of Rosenmüller which could not be removed surgically, he thought that radium or deep X-rays must be used. In the United States they had made considerable use of radium needles for many years. He remembered two years ago attending a meeting of the Academy of Medicine in Chicago when they talked about this problem, and their colleagues in Boston were all against using as much radium as they had been in the habit of doing. In Sweden they used a little deep X-ray therapy in those few cases where they could not get good results by surgery. Some fifteen years ago he made some investigations on the ciliary movements in cases in which he had done total resection of the upper jaw for cancer. After an application of radium they had no ciliary movements at all for years, and it might be the same if too much X-rays or radium were used in the nasopharynx.

Another point concerned the pituitary gland which also was very sensitive. If small radium needles were used, the distance could be better estimated, but if deep X-ray therapy was employed it seemed possible that damage might be done. As a rule in his clinic they only used deep X-rays or radium in cases where they had had bad results from surgical measures.

Mr. R. Scott Stevenson congratulated the President on emphasizing the importance of removing adenoids in children. He himself regretted to see junior surgeons devoting themselves so much to fenestration and similar procedures, to the neglect of the removal of tonsils and adenoids in children. The latter from the sociological point of view was much more important.

Mr. G. H. Bateman said that in his experience nasal sinusitis *per se* appeared to have remarkably little effect upon the eustachian tube or middle ear although it might affect this indirectly by causing enlargement of the adenoids.

Mr. Francis McGuckin thought that the effect of sinusitis on the eustachian tube might be influenced by the detailed anatomy of the uncinate process of the ethmoid. If this formed a deep gutter, pus might run down over the tubal orifice. If, however, the process was shallow pus tended to fall into the interior meatus and reach the post-nasal space beneath the tube.

Mr. Philip G. Scott said that in agreement with the views of his father he still found considerable value in the use of the eustachian catheter for chronic eustachian obstruction associated with vertigo and some cases of deafness.

Mr. Gavin Young stressed the importance of sinusitis as a cause of deafness persisting after adequate removal of the tonsils and adenoids.

Mr. Munro Black said that he had seen many cases who had had a considerable amount of treatment by radiation. Although one might assume that ciliary action had been suppressed, he had never seen any resultant ear trouble.

Dr. F. M. Allchin said that speaking as a radiotherapist there seemed to him to be some misconception as to the value and also the possible dangers of irradiation in the nasopharynx. This entirely depended first on a knowledge of what irradiation, either with radium or X-rays, would do when given in proper doses. It was quite wrong to think that the adequate and correct doses of radiation could do any permanent damage to the mucous membrane. If permanent damage was done it was an indication that the dosage had been too high. He had treated children from 7 to 15 during the past fifteen years at brief and fairly regular intervals in selected cases, and he had never yet had any permanent change or trouble with any of them. At times the sensitive cases, or those in which nasal catarrh was rather a prominent symptom, or again those in which there was possibly some local infection, would show a rather severe primary reaction, but with proper attention this nearly always died away.

With regard to the treatment of adults, this came into prominence during the war, with the treatment of flying personnel. Radium, which was very much favoured in America, was found, after careful physical measurement was made of the types of applicators and tubes used, to be highly dangerous, because the intensity of radiation from radium sources falls off extremely rapidly and therefore a series of doses was given in order to get rid of the excessive lymphoid tissue. This proved harmful to the superficial surfaces of mucous membrane, and of course completely destroyed the ciliated epithelium. Permanent damage had been produced in the eustachian tube itself by that method, which was later abandoned in favour of X-ray therapy, the X-rays being extremely carefully controlled.

The possibility of danger to the pituitary might in certain circumstances be very real, but if the size of field was the proper one he did not think that the dosage delivered to the pituitary was such as to make any difference. The irreversible action of radiation, which he had heard mentioned by one speaker, was a misnomer. A small dose of radiation on any tissue produced temporary change and after an interval the tissue returned to normal.

Section of Obstetrics and Gynæcology

President—V. B. GREEN-ARMYTAGE, F.R.C.O.G., M.D., F.R.C.P.

[*January* 19, 1951]

DISCUSSION ON CYTOLOGY IN THE DIAGNOSIS OF CANCER OF THE UTERUS

Dr. J. Bamforth: The examination of vaginal smears as a means of diagnosis in carcinoma of the genital organs is a rational procedure.

The development of this method of examination.—The smears used in the detection of malignant disease in the female genital organs are prepared by the wet-film method. The late Professor L. S. Dudgeon introduced it for the histological examination of fresh tissues over twenty years ago. In conjunction with Patrick (1927) and later with Barrett (1934) he published two papers giving an account of more than 1,000 tumours which had been examined in this way. The results obtained compared very favourably with those obtained from the examination of paraffin sections. Wrigley (1932) and Bowes and Barrett (1935) used this method in the diagnosis of lesions of the female genital tract. The technique used then is precisely the same as that used at St. Thomas's at the present time. The tissue which is removed at operation is not put into fixative or fluid of any kind but is incised as soon as possible and the fresh-cut surface is scraped with a sharp scalpel. A film is made and whilst wet is fixed immediately in Schaudinn's solution. After passing down the alcohols it is stained with hæmalum and eosin, cleared, and mounted with Canada balsam. Very beautiful preparations can be made by this method. As compared with paraffin sections the cells are much less shrunken, the details of nucleus and cytoplasm are more clearly shown. This is essential because the diagnosis depends on the cytological examination alone. Many pathologists believe that in the absence of invasion of the deeper tissues by malignant cells a diagnosis of malignancy cannot be made with certainty (Bland-Sutton, 1922). The experience of more than twenty years, however, both in this country and abroad has shown that there are certain characteristics of malignant cells themselves which distinguish them from normal cells. It is true that the cells of the most differentiated neoplasms show appearances which differ but little from those of normal cells but in the great majority of cases and in the numerous atypical and more malignant growths, the differences in appearance are considerable. It is true also that in certain cases chronic inflammation may lead to changes in cell appearance which give rise to difficulty. Considerable experience therefore is required before one can become efficient in this method of histological examination. Smears and sections from both normal and pathological tissues should be examined and compared and with continued practice considerable proficiency can be attained. A diagnosis of malignancy can be made from the cytological examination alone in an increasing number of cases. The main criteria upon which this diagnosis depends were originally described by Dudgeon and his associates and I cannot do better than quote from them. Dudgeon and Barrett (1934) considered that "malignant cells stain more deeply than their benign prototype. This is due to the fact that the nuclei have a greater affinity for hæmalum. They vary in size and shape, they are larger than normal and their position relative to the surrounding cytoplasm is in no way constant. The nuclear chromatin is arranged in thick irregular and deeply staining bundles and the fine reticular arrangement of normal cells is rarely seen. The nucleoli are much larger than normal, they are sometimes multiple and stand out as purple or pink dots in the sphere of the nucleus".

It was obvious that the wet-film method of histological examination was capable of wide application and using the same simple technique Dudgeon turned his attention to the examination of certain pathological fluids, urine, sputum, ascitic and pleural fluid and stomach washings. Meanwhile, in the United States of America Papanicolaou had been engaged for many years in the study of the cellular content of vaginal smears. As long ago as 1928 he had discovered cancer cells in the human vaginal smear. Some years later, in conjunction

with other workers, he published a number of papers on this subject in relation to both normal and pathological conditions and especially as a method of diagnosis of malignant disease in the female genital tract (Papanicolaou and Traut, 1943). This procedure has become very popular in the United States. Everywhere it is agreed that the vaginal smear is not intended to replace the biopsy specimen from the cervix or body of the uterus. It is regarded as a preliminary or complementary method of diagnosis and as such can be used as a screening process in the examination of large numbers of patients. If a positive or suspicious result is obtained the patient should be examined very carefully and a biopsy taken. It may be necessary to repeat this procedure. Experience has shown that certain cases of malignant disease which were missed in the clinical examination—including even the use of biopsy—and which might have remained undiagnosed for some time were first detected by the vaginal smear. The importance of early diagnosis in malignant disease and especially in cancer of the cervix is obvious to all. We therefore began to study smears from the vagina and from the cervix. I find that the examination of these smears for malignant cells is harder than that of smears from sputum and considerable practice will be necessary. It is easier to carry out further investigations in gynæcological cases than in the case of suspected lung carcinoma and so in reporting a vaginal smear a third report "suspicious" is permissible and indeed is largely used in the U.S.A. Especially is this important in relation to cases of very early carcinoma and in the condition of intra-epithelial carcinoma where it may be difficult to decide where to take a biopsy, if indeed to take one at all. Judging by the reports in the literature these cases appear to be increasing in number.

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Mr. C. S. N. Swan and **Dr. K. R. Dempster:** The object of this paper is to describe our experiences in the examination of vaginal and cervical smears from 400 specially selected patients in relation to cancer of the uterus. Smears have been taken from those complaining of irregular bleeding or discharge or both, or in whom some obvious cervical pathology has been found. At the beginning of the investigation a number of cases was examined by Dr. W. M. R. Henderson using smears obtained mainly from the posterior fornix with a platinum loop. In the majority, however, smears were made also from the cervix with Ayre's spatula, by means of which a circular surface biopsy is obtained. We consider that the examination of smears from both vagina and cervix is essential. It is better to obtain the vaginal smear first as the cervical scraping often causes bleeding. The method of preparation is the routine method used at St. Thomas's Hospital for staining smears made from tumours, sputum and other pathological fluids for the diagnosis of malignant disease. The smears are fixed in Schaudinn's solution and stained with hæmalum and eosin (Dudgeon and Barrett, 1934). We have found, as have other workers, that an estimate of the phase of the menstrual cycle can often be made by the vaginal smear. The appearances of the follicular phase are usually distinctive. The cornification of the superficial epithelial cells is marked and their nuclei small and pyknotic. The absence of polymorphonuclear cells is striking. We have found, however, that a cervical scraping from a case which gives a clean preparation in the vaginal smear shows many polymorphonuclears although the cervix appears normal. It is usually found that there are many more polymorphs in the cervical smear than in that from the posterior fornix. In the diagnosis of malignancy we have been guided by the criteria already referred to by Dr. Bamforth. Our reports have been classified into three categories: (1) no evidence of malignancy; (2) cells suspicious of malignancy; (3) malignant cells present suggesting either squamous or columnar celled carcinoma. We regard a positive or a repeatedly suspicious smear as an indication for further investigation. As the cervical smear is taken by rotating Ayre's spatula through 360 degrees around the squamo-columnar junction it is impossible to be certain from which part the suspicious cells are derived. If clinical examination reveals a definitely suggestive area or areas local biopsy may be performed. Other workers have found that in some cases it is difficult or impossible to decide where to take a biopsy. A circular or cone biopsy has therefore been recommended. The tissue removed can be examined in a number of sectors and should a suspicious area be found by the microscope, serial sections from the particular sector can be made. We have found that in performing a cone biopsy it is better to use a curved bistoury rather than diathermy owing to the heat coagulation produced by the latter. All cases yielding a suspicious smear on repetition should have a curettage of the cervical canal and body of uterus.

The results are shown in Table I. The number of cases reported as positive or suspicious in which no further evidence of malignant disease has been found is large but these are due

TABLE I

Total number of cases examined			400
Smear diagnosis: negative			330
Subsequently found malignant			nil
Smear diagnosis: suspicious		24	
Proved on biopsy malignant (including one intra-epithelial carcinoma of cervix)	2		
Cystic hyperplasia of endometrium	9		
Cervical polypi and chronic cervicitis	6		
No evidence of malignancy	4		
Not yet fully investigated	3		
Smear diagnosis: positive			35
(*a*) squamous-celled carcinoma confirmed by biopsy	29		
Following cervical irradiation for known carcinoma	1		
Biopsy: no malignancy found	4		
Not yet fully investigated	1		
(*b*) columnar-celled carcinoma of body			11
Confirmed by biopsy	6		
Biopsy: no malignancy found	5		

to sources of error which are shown in the Table and have been encountered by other workers. During the last six months, we have had no errors in the smears on which we have given a positive diagnosis of squamous-celled carcinoma.

Of the 31 proven cases of squamous carcinoma of cervix, 26 were regarded as clinically positive or suspected, whilst the remaining 5 were not suspected in the first place. Two of these 5 cases are described.

Case I.—Woman, aged 61, who had had one child and had worn a ring for twelve years. She had noticed a blood-stained discharge insufficient to necessitate the use of a pad. The cervix was large, with a large bleeding area on the anterior lip which was thought to be traumatic. Smears were reported as positive for squamous carcinoma of cervix. A biopsy was taken from the raw area on the cervix and the cervical canal curetted. Squamous-celled carcinoma was found in the curettings only.

Case II.—A nulliparous married woman, aged 30, complained only of a brownish intermenstrual discharge for three months. No abnormalities could be found on careful pelvic examination. The cervix showed no break in its epithelium. Suspicious cells were found in the cervical smears on two separate occasions and for this reason a cone biopsy of the cervix was done. Sections were prepared from all parts of the specimen and microscopical examination showed that a condition of intra-epithelial or non-invasive carcinoma was present. The histological appearances of this lesion and the cytological findings are shown in the accompanying photomicrographs. Fig. 1 shows an area of non-invasive carcinoma. Both superficial and deep cells show very atypical appearances. How different these appearances were is shown by the abnormal giant-cell types seen in Fig. 2 from another early focus

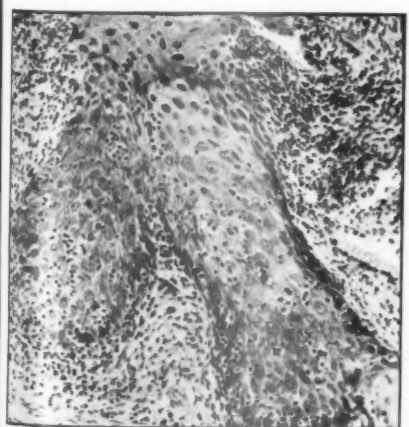

FIG. 1.—Area of intra-epithelial carcinoma found in biopsy from Case II, showing atypical superficial and deep cells. × 100.

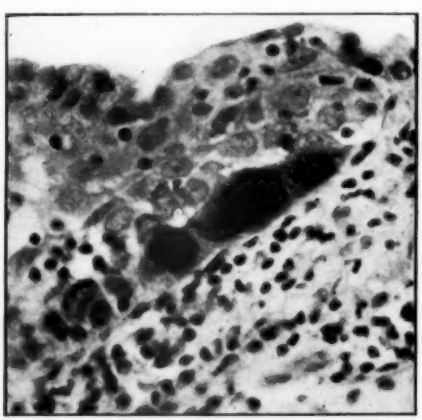

FIG. 2.—Another area from Case II, showing cells with giant, hyperchromatic nuclei. × 435.

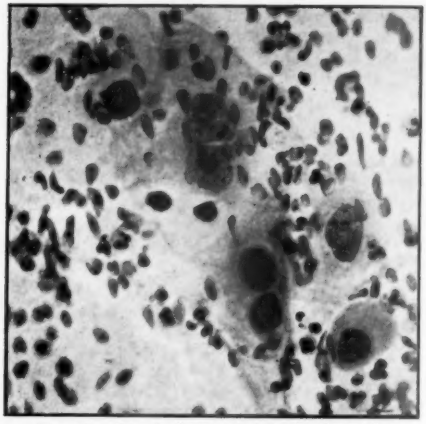

FIG. 3.—Atypical superficial cells found in cervical scraping from Case II. × 435.

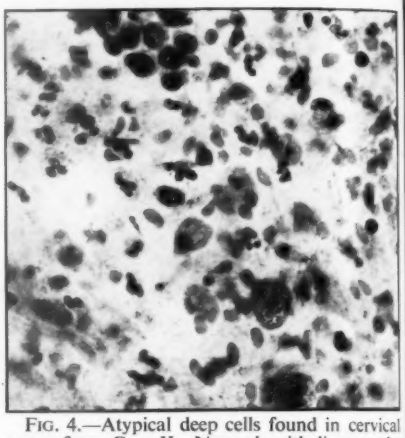

FIG. 4.—Atypical deep cells found in cervical smear from Case II. Normal epithelium at the top. × 435.

of intra-epithelial carcinoma. Both superficial and deep cells from this lesion were found in the smears (Figs. 3 and 4). Similar results were obtained by others (Skapier, 1949). In many of these cases described in the literature further sections have shown areas of definitely invasive cancer but this was not found here.

The fact that we have found in this small series several cases of clinically unsuspected malignant disease has given us encouragement. It is true that the majority were easily diagnosable by clinical examination and biopsy. Nevertheless, with the object of gaining experience, and for comparison between the cytology of the smears and that of the sections, it is important to examine smears from these cases also. Owing to the difficulty of obtaining sufficiently trained personnel we have restricted ourselves to examining smears from patients with definite and significant symptoms.

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Dr. A. F. Anderson, Dr. Marie P. S. Grant and **Miss Rhona M. McBryde** (*Department of Obstetrics and Gynæcology, University of Edinburgh*): The Edinburgh material is based on the work of the laboratory in the gynæcological department of the University, where reports on specimens from approximately 5,000 cases are issued annually. This affords a rich experience of gynæcological pathology from which we had culled three significant cases of cervical carcinoma-in-situ, not treated originally for cancer owing to misinterpretation of the histological picture, and all eventually developing invasive cancer (Anderson, 1950). Stimulated by Foote and Stewart's (1948) beautiful mapping of 27 cases of carcinoma-in-situ, clearly demonstrating the inadequacy of a single biopsy, and by the large sample of the cervical junctional epithelium afforded by a "ring" biopsy as advocated by Ayre (1948), we began to examine all cervices sent to the laboratory for routine histological report by this latter method and a worth-while number of unexpected early superficial cancers were discovered. It became very evident that these early growths and the cytological diagnosis as propounded by Papanicolaou and Traut (1943) were inseparably linked, just as it had become evident that the diagnosis of the earliest cancers was the only way of reducing the mortality of this all too common scourge (Maliphant, 1949).

We applied the method chiefly to the cervical cancer because it is the commoner, and because the endometrial cancer was admittedly more difficult to discover by smear interpretation. Ayre's (1947) surface biopsy spatula was used, as it seemed reasonable that it should produce better results, and avoid the latency of the small proportion of growths which are sometimes alleged not to exfoliate their cells into the posterior fornix. It has to be realized that this sampling of the entire junctional epithelium must be carefully performed, and that the smear obtained is not of desquamated cells, and is not designed to find endometrial cells (a fact which largely explains the majority of our "false negatives").

Our first thousand cases were taken from gynæcological out-patients, but not routinely, and the average age of the patients was 42 years. Generous facilities were afforded us, of reading the patient's case notes, while subsequent follow-up with review of many of the smears, led to the assessment of our work, as shown in the following explanatory tables, based on one cervical smear from each case.

TABLE I.—ANALYSIS OF A THOUSAND PATIENTS SCREENED BY ONE CERVICAL SURFACE SMEAR

Interpreted as	Negative (182 still to be admitted to hospital)	865
	Positive—correct for cancer (18 cervical, 3 endometrial)	21
	Positive (5) or suspect (10)—incorrect	15
	Suspect—and still *sub judice*	8
	Negative—incorrect for cancer (3 cervical, 8 endometrial)	11
	From known clinical cancers (49 untreated, 31 treated)	80
		1,000

"False positives" = 5 of 26 = 19·2%
"False negatives" = 11 of 876 = 1·25%

TABLE II

CORRECT POSITIVES		Average age
Pre-invasive epidermoid cancers of cervix	8	44·4 years
Invasive epidermoid cancers of cervix	9	53·8 years
Invasive adenocarcinoma of cervix	1	
Adenocarcinoma of endometrium	3	
	21	
By clinical examination		
Unsuspected	11 = 1·1%	
Regarded as possible	4	
Regarded as probable	6	
	21	

TABLE III

"FALSE NEGATIVES"		Comment
3 epidermoid cancer, cervix		All tiny pre-invasive growths All three unsuspected by clinician Review of smears showed one error; the other two smears were too thin, and still not positive
8 Adenocarcinoma, endometrium	1	Curettings only, malignant. No growth found in uterus later
	1	Had had a positive *vaginal* smear three months before this series. She defaulted and when she presented for curettage, a *cervical* smear was negative
	1	Negative on first attendance; positive when admitted for curettage
	5	Review of these still failed to find definite cancer cells, and very few that were suspicious

TABLE IVA.—"FALSE POSITIVES" AND "SUSPECTS" FOR CERVICAL CANCER

5 actually termed "positive"	Cervical biopsy showed no cancer in 4. Interpretation six months later was negative. And one error was due to radiation change In the fifth case the biopsy showed a borderline picture. Smear interpretation agreed to by Dr. Ayre
4 termed "suspicious"	Cervical biopsy benign in all 4. Interpretation six months later was negative

TABLE IVB.—"FALSE SUSPECTS" FOR ENDOMETRIAL CANCER

Histological check	Comment
1 "No curettings obtained"	Smear still suspect on review. Patient died of carcinomatosis 3/12 later. No autopsy. "Not proven"
2 Metropathia hæmorrhagica	Actual report "endometrial cancer or hyperplasia". Review of smear now = negative
3 Benign curettings, and cervical polypus	Review of two smears = one suspect cell in each. Not enough
4 "No curettings obtained"	Review of smear = negative
5 Metropathia hæmorrhagica	Review of smear = still some puzzling cells
6 Hysterectomy = benign uterus	Smear almost invisible, still has some atypical cells on review

TABLE V.—*Sub Judice* CASES

Review of These Smears Still Leads to Suspicion

2	Biopsies of cervix benign, but small and not samples of entire junctional epithelium
2	Suspect of endometrial malignancy but curettings inadequate for any opinion
3	No histological confirmation as yet
1	Almost "conclusive". Ring biopsy admitted to be difficult and was inadequate, though one small area was borderline. Later smears have been negative, but are being taken monthly

One case is deemed sufficiently striking to report. It was that of a woman of 40 who did not return for a follow-up visit after cauterization of the cervix. A smear was taken prior to cauterization and found to be positive, but reported only after she had been discharged. It was a whole year before she could be persuaded to return for biopsy, and the cervix appeared to be normally covered by epithelium. A cone biopsy, however, revealed a tiny superficial growth with equivocal invasion, in two out of the twelve blocks made from it. After extended hysterectomy, the remainder of the cervix was sectioned very thoroughly but no more growth discovered (Figs. 1 to 5).

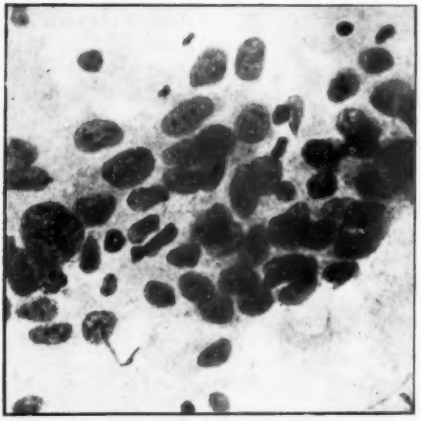

FIG. 1.—Cluster of malignant cells in cervical smear before cauterization, November 1949. × 520.

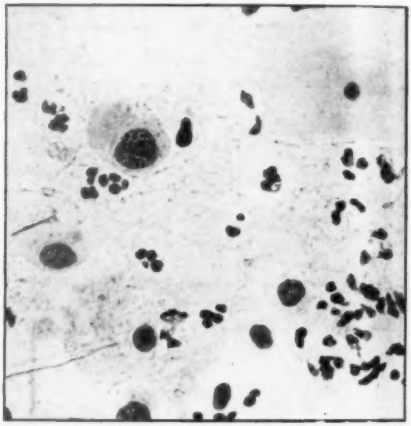

FIG. 2.—Malignant squamous cells from the same smear as Fig. 1, with pyknotic nucleus of a benign squama at top right. × 520.

DISCUSSION

We believe that because of the accessibility of the cervix and with increased experience in interpretation of smears, and of skill in taking them, the majority of early superficial cancers can be discovered. If there is a "target" lesion, then logically a biopsy best establishes its nature; but, without it, only a sample from the entire circumference can exclude malignancy. This sample may reasonably be expected from the smear technique, but if experienced clinical suspicion is strong, a negative smear should not be regarded as final, and a ring biopsy should be taken; similarly if the smear is positive, but there is no "target" area, a ring biopsy should be taken and the endocervix also curetted. It is worth noting that a brisk post-menopausal bleeding is unlikely to come from a pre-invasive cervical cancer, which carries no blood vessels in the superficial epithelium, and that in such cases where the cervix appears to be healthy, a vaginal smear is the more likely to find an endometrial cancer; but we find also that such cases are admitted so quickly to hospital as to gain no acceleration of their diagnosis and treatment by smear interpretation, and curettage is still the most exact path of diagnosis.

There is, of course, no excuse for radical treatment based on a positive smear alone; the smear technique is a technique for finding patients for definitive biopsy, or curettage, and is not in itself diagnostic.

It was admitted originally that vaginal as well as cervical smears should be done on each patient, but this was not possible and we are now concentrating on cervical cancer with routine screening of all gynæcological out-patients. In any case we do not believe that curettage can be omitted in any case of suspicious menstrual irregularity, because of a negative smear.

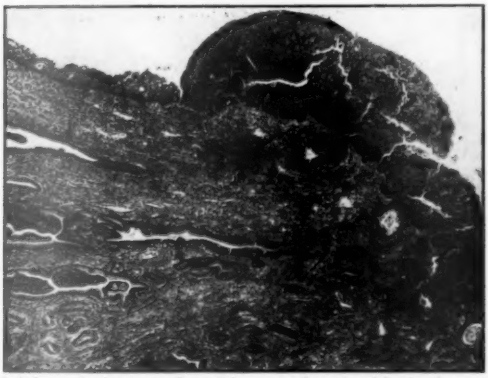

FIG. 3.—Early superficial cervical cancer found in one of twelve blocks from "ring" biopsy. × 26.

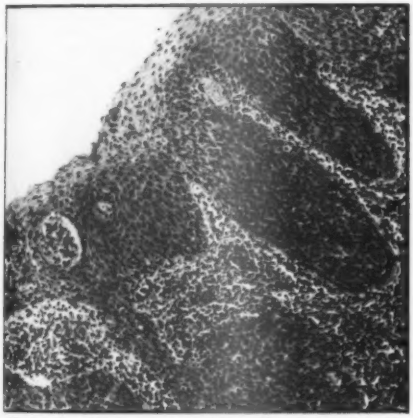

FIG. 4.—High-power view of cancerous epithelium from same biopsy as Fig. 3 but a different area. × 108.

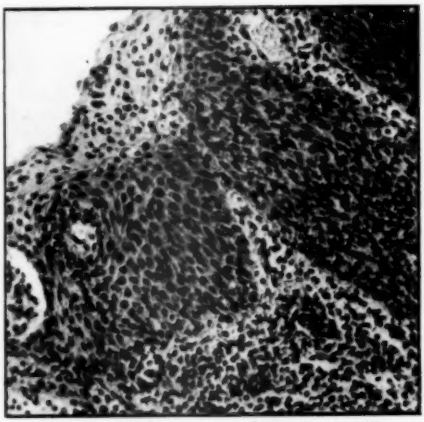

FIG. 5.—Higher power of Fig. 4. × 183.

Of the cervical cancers we believe we will find more by taking smears routinely from all cervices, rather than by selecting those in suspicious cases. If we select, we will miss the pre-clinical cancers which are microscopic, and may be present in an apparently healthy cervix.

SUMMARY AND CONCLUSIONS

(1) In a series of 1,000 patients from whom cervical surface smears were obtained, 11 clinically unsuspected cases of cervical cancer (1·1%) were discovered, and 8 of these were of the pre-invasive type. 7 others, also discovered, were regarded clinically as possibly or probably malignant, but requiring biopsy.

(2) Three endometrial cancers were found in cases clinically suspicious, for which diagnostic curettage had been arranged.

(3) False "positive" smears were 5 out of 26 (19·2%), and false "negatives", 11 out of 876 (1·2%). 8 cases remain *sub judice*.

(4) The following conclusions were arrived at: (*a*) That the cervical smear technique is capable of discovering early cancers of the cervix before they are recognizable clinically.

(*b*) That the method has a special advantage in centres where the waiting list for hospital admission is large, though a negative smear report should not be weighed against an experienced clinical suspicion calling for biopsy. The method is not diagnostic.

(*c*) That radical surgery or radiotherapy is not justified on the grounds of a positive smear report alone.

(*d*) That endometrial cancer, in view of its considerably lesser incidence, and its acknowledged greater difficulty of interpretation, than cervical cancer, is still better searched for by diagnostic curettage, which should never be omitted simply because the smear report is negative.

(*g*) That the best results will be obtained by applying the smear method chiefly to the problem of cervical cancer.

We wish to thank Professor Kellar for stimulating the work in the first place and ever since, and to acknowledge that its interest was assured by the co-operation he and Dr. E. C. Fahmy gave us, in making us welcome in their wards, and with their records, without which the work would have been impossible.

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Dr. Erica Wachtel: During the past two and a half years routine screening for uterine cancer has been carried out in the Hammersmith Hospital on every woman attending the Gynæcological Out-patients' Department or admitted to the gynæcological wards.

The fact that uterine and vaginal carcinomata can be recognized by smear examination is to-day fully appreciated. Good results can only be obtained by expert interpretation of well-stained slides and also by a satisfactory technique of taking the smears. The latter is usually done by the junior staff who, unless taught differently, are inclined to regard the matter as an unimportant technical detail. It stands to reason that results can only be accurate when the smear is composed of a representative number of exfoliated cells which have been spread out over the slide in such a way that the individual cells can be viewed in detail under the microscope.

In the Hammersmith Hospital we prefer the aspiration method from the posterior fornix because material coming from this pool contains exfoliated cells from the cervix as well as the corpus uteri and because the method is simple, clean and painless.

The number of exfoliated cells depends on the proliferative activity of the tissues as well as on the size of the exfoliating area. Malignant growths have a greater proliferative activity than normal tissues but their surface area is, as a rule, considerably smaller than that of normal tissues. This explains why cancer cells are usually not found at a glance but have to be searched for painstakingly.

A certain and fortunately small percentage of cancers fail to exfoliate at all or do so only to a minimal extent and these account for the inherent source of error. However, as this chiefly concerns advanced and well-established carcinomata, this diagnostic failure is more of an academic than a practical interest.

Cancer cells found in vaginal smears can be squamous or endometrial in origin and are either differentiated or undifferentiated. Malignant cells in general are recognized by their nuclei which are enlarged, often hyperchromatic and contain coarse, irregular chromatin granules.

There are three varieties of differentiated squamous carcinoma cells, viz.:

(*a*) Malignant fibre cells which are elongated thin cells with enlarged hyperchromatic nuclei filling the major part of the cell volume (Fig. 1).

(*b*) Tadpole cells which resemble amœba and have very large, hyperchromatic nuclei with coarse chromatin granules varying in size and shape. Many are multinucleated (Fig. 2).

(*c*) Malignant basal cells resembling normal basal cells but having enlarged nuclei with malignant features (Fig. 3).

In contrast to these definite patterns in which differentiated squamous cancer cells are seen, undifferentiated squamous cells vary in appearance and cannot be classified. They usually appear in clusters. Their origin can only be established if a few differentiated cells are also found, which is usually the case. Their malignant nature is diagnosed by the nuclear structure; absence of cellular borders as well as great variation in size and shape of the individual cells distinguish them as undifferentiated cancer cells (Fig. 4).

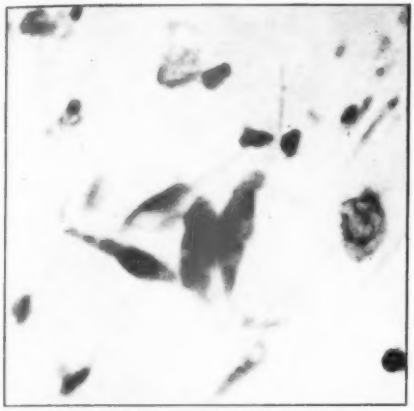


FIG. 1.—Malignant fibre cells from early invasive squamous carcinoma. × 900.

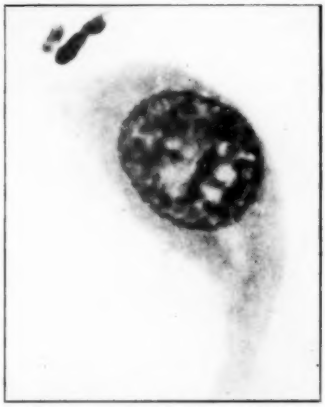


FIG. 2.—Tadpole cell. × 1150.

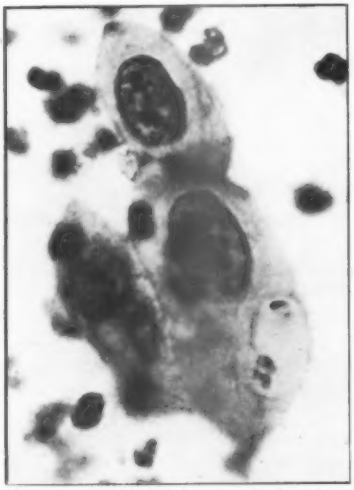


FIG. 3.—Malignant basal cells from a case of carcinoma-in-situ. × 875.

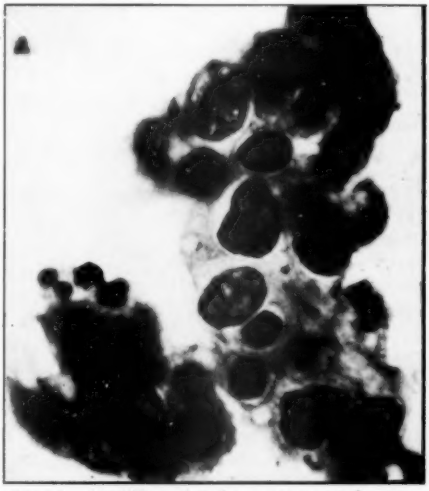


FIG. 4.—Undifferentiated squamous carcinoma cells. × 875.

Contrary to the current statement in the literature we found the diagnosis of adenocarcinomata easy because of their tendency to exfoliate in clusters and the uniformity of appearance of the exfoliated cells. The differentiated adenocarcinoma cell looks like the normal endometrial cell but has a "malignant" usually eccentric nucleus, an abnormal nuclear/cytoplasmic ratio and apparent though not very sharp cell borders (Fig. 5).

Undifferentiated malignant endometrial cells are seen in tight clusters of which usually only the nuclei are apparent, as cellular borders are not distinguishable (Fig. 6).

A critical review of the results of screening is, I think, a direct answer to the important question of the reliability of this form of cancer detection. From January 1 to December 31, 1950, 1,244 smears from 946 patients were examined. 22 of these patients were found to suffer from uterine cancer which gives an incidence of malignancy of 2·32%.

Of these 22 histologically verified cancers 12 were adenocarcinomata and 10 squamous malignancies. 20 of these or 90·9% had positive smears and 2 (histologically adenoacanthomata) had been missed. 4 of these positive cases or 18% were picked up by screening

and would otherwise probably have passed unnoticed until the lesion had progressed sufficiently to cause clinical symptoms and signs. In 2 of these the first biopsy reports were negative and the diagnosis was histologically verified only at a later date. One similar case (positive smear, negative biopsy) is still under observation and has not been included in this series. Two false positive reports were given.

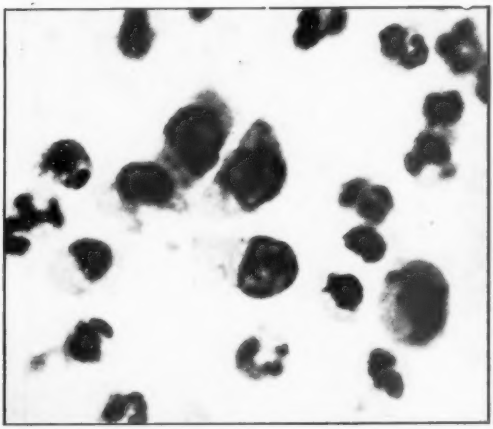


FIG. 5.—Differentiated adenocarcinoma cells. × 1050.

FIG. 6.—Undifferentiated adenocarcinoma cells (relapse after radium treatment). × 1050.

CONCLUSIONS

(1) We found the vaginal smear to be a very useful method for spotting early, clinically unsuspected cancer.

(2) A negative smear does not exclude malignancy and should not create a feeling of security.

(3) A positive smear must be taken seriously and indicates the necessity for a close follow-up.

(4) Smear and biopsy are complementary methods to an identical aim. Neither is perfect and both should be employed.

I wish to thank Professor Kellar for kindly allowing me to use the photomicrograph of the tadpole cell.

Section of Psychiatry

President—E. O. Lewis, D.Sc., M.R.C.S.

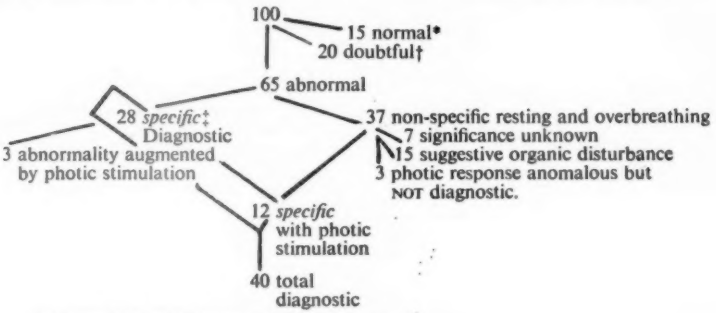
[*November* 14, 1950]

DISCUSSION ON RECENT ADVANCES IN THE EEG DIAGNOSIS OF EPILEPSY

Dr. W. Grey Walter (Burden Neurological Institute, Bristol): During the last fifteen years electroencephalography has evolved from a laboratory curiosity into a practical diagnostic aid. Many of the early hopes have been richly fulfilled—on the other hand some of the early confidence has been dissipated. From the physiological standpoint the information gained during this epoch is of enormous interest; indeed one may now speak quite reasonably of the physiology of paroxysmal disorders.

As always there is a statistical and an experimental approach. It is with the latter that I am mainly concerned but it may be as well to scan briefly some figures culled from the records of an EEG department, in order to appraise the value of the method to clinicians.

Since 1942, when quantitative methods of analysis were introduced, about 8,000 patients have been examined; many of them several times. Of this clinical population about 75% have been referred because of seizures; that is, in the EEG files they are classed as "? epilepsy". This number, about 6,000 patients, does not include any whose attacks are believed by clinicians to be due to a known intracranial lesion, but many of course—



*"Normal" here includes weighting for age.

†"Doubtful" includes asymmetries, unusual distribution of normal components, immaturities, frontal "alphoid", transient theta rhythms and the like.

‡Specific here means diagnostic of "idiopathic" epilepsy—wave and spike, sharp and long waves, spikes—while resting or during overbreathing.

FIG. 1.—Percentage statistics of EEG findings and results of photic activation in 2,000 cases of patients complaining of fits.

particularly during the war years—had a history of head injury. Over this whole period about 55% of these patients complaining of fits gave EEG records which we classed as "abnormal" but less than half of these abnormalities, 25% of the total, were regarded as strictly diagnostic of epilepsy or intracranial disease. There is a marked correlation with age; only a few hundred of the diagnostic records were in patients over 30 and in many of these the findings were suggestive of a local intracranial lesion. The figures up to four years ago are analysed in detail in the book "Electro-encephalography" edited by Hill and Parr (1950); since the time when this was written various activation procedures have been brought into operation and the clinical value—as well as the scientific interest—has increased. One may now say that in 100 patients complaining of some sort of attack or attacks, the resting and overbreathing records of about 85 will show some abnormality—of these, 20 will be indefinite, consisting of asymmetries, immaturities and the like, and 65 definitely outside the normal range (Fig. 1).

Of the 65 abnormal cases 28 will show specific features, but 37 without activation will be non-specific. The most important advance in the statistical sense is that of these 37 non-specific abnormalities, 12 will be converted by photic stimulation into specific patterns; so that of the whole 100 patients complaining of fits, 40% may now be expected to yield diagnostic patterns in the EEG if we include the results of photic activation—which, incidentally, do not show as marked a correlation with youth as do the findings during rest or overbreathing.

Before dealing with photic activation in more detail, certain features of the resting records which have been revealed only by the prolonged and repeated study of this large clinic should be discussed. Some patients have been followed for fifteen years and from them of course scores of records have been taken. It has been possible in these patients to follow the various epileptic manifestations during maturation and to observe the effect of the several forms of treatment introduced from time to time.

Perhaps the most disturbing observation is that many patients, in whom originally a focal disturbance was found, have later developed non-focal activity of the "classical wave-and-spike *petit-mal*" type. So-called "focal sharp waves" often accompanied by much slower waves—what some American workers call the "*petit-mal* variant"—after many years can turn into the classical bilateral synchronous wave and spike which all regard as characteristic

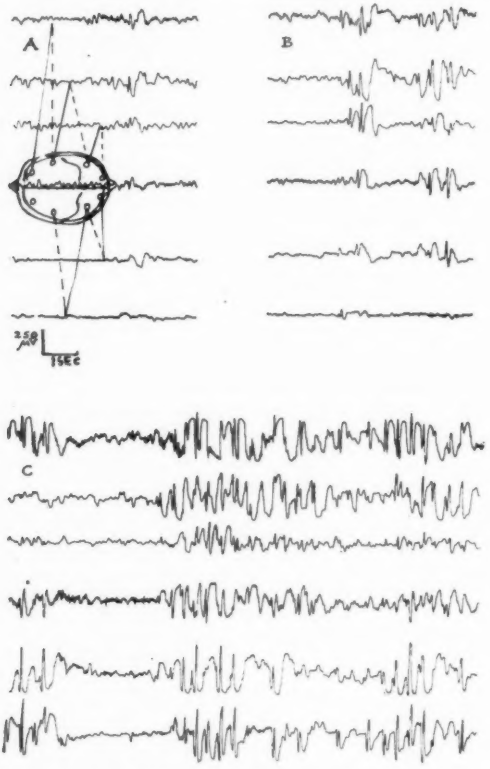


FIG. 2.—Evolution of bilateral synchronous wave-and-spike from right temporal sharp-wave focus in a girl aged 5 at time of first record. A taken in 1948, B in July 1950, C in October 1950. History of major attacks once a month, increasing in severity, starting on left side, originally attributed to worms.

of *petit mal* (Fig. 2). This throws a clear though oblique light on the recent theories of paroxysmal disorders. It certainly suggests that the choice of subjects for surgical intervention is much less straightforward than was at first supposed. It is interesting also that patients with a sharply focal disturbance of the sharp-and-slow-wave type may be found

a few months later to have a precisely similar disturbance in an entirely different part of the brain, sometimes in the homologous region of the other hemisphere, but often in quite unrelated areas. In some cases the evolution of wave-and-spike from focal sharp-and-slow waves may be demonstrated experimentally by photic stimulation—which again is evidence in favour of the theories of epilepsy discussed elsewhere (Walter in "Electro-encephalography", 1950, Walter 1947, Walter and Walter, 1949*a* and *b*).

The physiological basis of the activation procedures which have so much interest and value in the clinic is a sound development from experimental observations and it is comforting to recall that the effect of rhythmic photic stimulation was not an accidental discovery.

In 1942 we observed that automatic frequency analysis of epileptic records *between* seizures often displayed components which were harmonically related, or nearly so. During the seizures themselves the harmonic relationship was closer and more consistent, as would be expected from the regularity of the seizure patterns. With the aid of models we demonstrated that the various epileptic waveforms could be synthetized from simple sinusoidal components, and that very slight maladjustment of amplitude, frequency or phase would destroy the diagnostic pattern, turning it into something more like the inter-seizure records whose significance was first detected by frequency analysis. It was also pointed out that even the most widespread and synchronous seizure patterns appeared different in different areas, indicating that the various components were in fact local though interdependent phenomena (Walter, 1947).

From these observations it was predicted that if *by any means* one or more of the resting components could be augmented and made to synchronize the others, a seizure pattern might develop. From this it was a simple step to experimentation with photic stimuli, which were known to be by far the most effective in the evocation of normal cerebral responses. The first wave-and-spike pattern was evoked in this way in 1945 and the relation of the effective frequencies and the resting rhythms was precisely as predicted from the earlier observations.

Since then, clinical observations of a more or less routine nature have been supplemented by experimental studies, both of humans and of animals, the latter notably by Gastaut and his colleagues. The evidence strongly suggests than when volleys of impulses appear in the visual afferent pathways at certain group frequencies, there is a strong tendency for their effect to extend through the structures around the third ventricle in such a way that they can influence almost any of the thalamic and hypothalamic nuclei as well as the reticular formations which are only now being thoroughly investigated. In some cases this leakage can only occur when the parieto-pulvinar-occipital circuits are in a certain state. In these cases the evocation of epileptic patterns occurs only when flicker stimulation is applied precisely at the moment of closing the eyes (Figs. 5 and 6). The degree and certainty of activation in such cases depend upon the condition of many subcortical structures and if small quantities of a convulsant drug are injected, flicker stimulation will produce epileptic phenomena in any human or any animal even when the dose of the convulsant is only about one-tenth of that required to produce a seizure by itself.

The most striking and consistent feature of epileptic records during photic activation is the generation of subharmonics of the stimulation frequency. On theoretical grounds this seems a quite pointless mechanism and indeed it is probably almost wholly pathological, but such a process would be expected to occur as a peculiar fault in a system designed for the setting up of conditioned reflexes, and it is worth considering the possibility that this "counting-down" effect may be due to disturbance of one part of the elementary learning mechanism represented by the diffusely projecting structures around the third ventricle. The pathological effects of photic activation are extremely difficult to condition, in spite of their amplitude and regularity; it is tempting to suppose that this may be because of the nature and location of the effects themselves.

From the strictly diagnostic standpoint, photic activation seems to yield four main classes of specific abnormality. The first and most common is a diffuse activity at moderate potential with many poorly synchronized components; what is sometimes called a dysrhythmia (Fig. 3). This usually builds up slowly during stimulation and is always accompanied by disagreeable subjective sensations of an indefinable nature. It is most commonly evoked by flicker at a frequency of 16–24 f/s. This range of frequencies is the "magic" one for epileptic activation and adjustment to the precise frequency is often very critical (Fig. 4). There is good evidence that in many cases the important factor is the *interval between flashes* as well as their frequency. In some patients two flashes only will evoke a diagnostic pattern, provided that they are separated by about 60 milliseconds (Fig. 5). This interval appears to be the period of maximum facilitation in physiological conditions, even for somatic sensory volleys, and in many epileptics the phenomenon may be considered a physiological misfortune. In some cases the activation appears only when the flash rate is

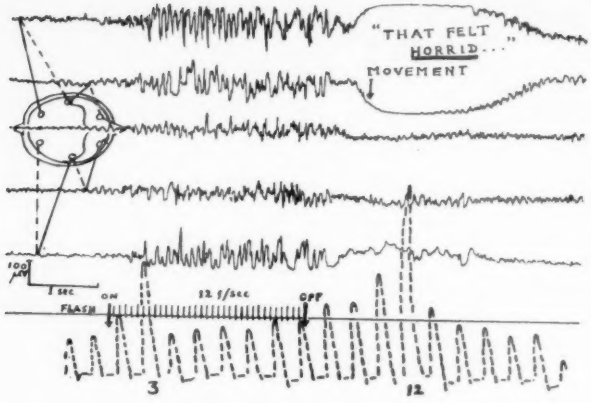


FIG. 3.—"Dysrhythmia" evoked by flicker at 12 f/s in "hystero-epileptic" female aged 24. Prolonged stimulation precipitated a tonic-clonic major convulsion. Note the response at the flash frequency and its fourth subharmonic, together with a wide distribution of activity over the whole spectrum. The resting records were abnormal but not diagnostic.

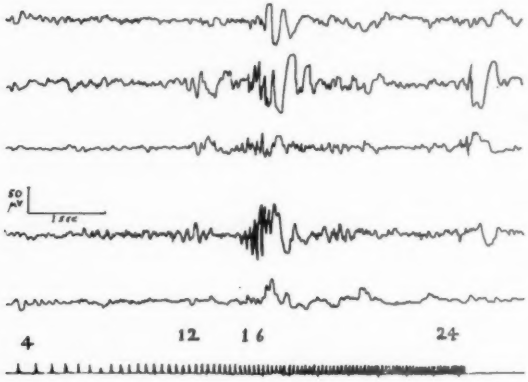


FIG. 4.—Variation of evoked activity with frequency of stimulus in epileptic man aged 20 with history of occasional major attacks for ten years. Stimulation at 12 f/s evokes only exaggerated elementary response and a slow wave; at 16 a crescendo of sharp waves ending in a diffuse slow wave; at 24 one spike followed by a slow wave. The resting records were normal. Electrodes as in Fig. 3.

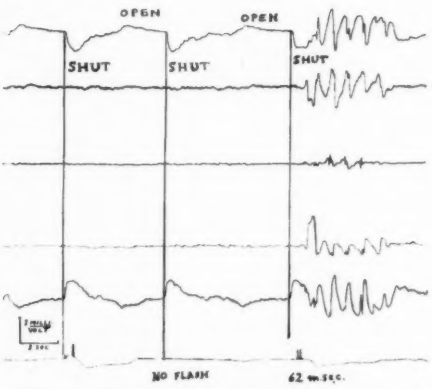


FIG. 5.—Diagnostic pattern evoked only by two flashes during eye closure in boy aged 6 with history of one major followed by several minor attacks. Shutting the eyes without stimulation was ineffective, nor did a single flash evoke any abnormality. The effective flash interval was between 55 and 65 m.sec. The resting records were normal. Electrodes as in Fig. 3.

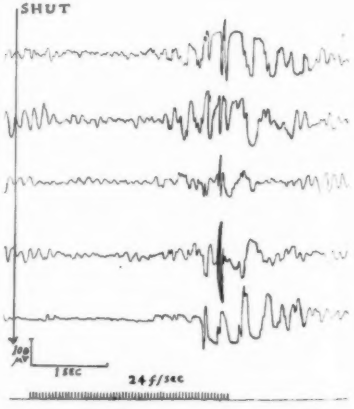


FIG. 6.—Wave-and-spike evoked by flicker during eye closure at 24 f/s in boy aged 14 with history of "blackouts" monthly for one year. Resting records abnormal but not diagnostic. Electrodes as in Fig. 3.

varied rapidly within the critical range, or when several flicker sources are used simultaneously (as Hodge will describe in more detail), or again may require synchronization of the flash with some component of the EEG itself: the trigger-feedback method described elsewhere (Walter, Dovey and Shipton, 1946; Walter, 1947; Walter and Shipton, 1949; Walter and Walter, 1949*a*, 1949*b*; Corriol and Gastaut, 1950). Turton and Hewlett have used this method with considerable success as an aid to routine diagnosis.

This evoked dysrhythmia is sometimes the precursor of a more definite pattern; whether or not the various components fall into step depends upon the skill and patience of the operator and upon the precise state of the patient; successful medication is often reflected in a persistent failure of the dysrhythmia to coalesce into a specific pattern. The length of after-discharge is also variable and significant.

The second type of evoked abnormality is the wave-and-spike. This also is most readily evoked at flash frequencies between 16 and 24 and in some cases only when stimulation in this range is provided just at the moment of closing the eyes (Fig. 6). In this group of cases there is always some after-discharge; the slowest components persist longest, the spikes often disappearing a few seconds after the end of the flicker. As already mentioned the wave-and-spike pattern may be preceded by a diffuse dysrhythmia—the two conditions are far from exclusive.

The third type of abnormality is the evocation of large brief spikes in the central and frontal areas, accompanied by myoclonic jerking of the musculature (Fig. 7). This

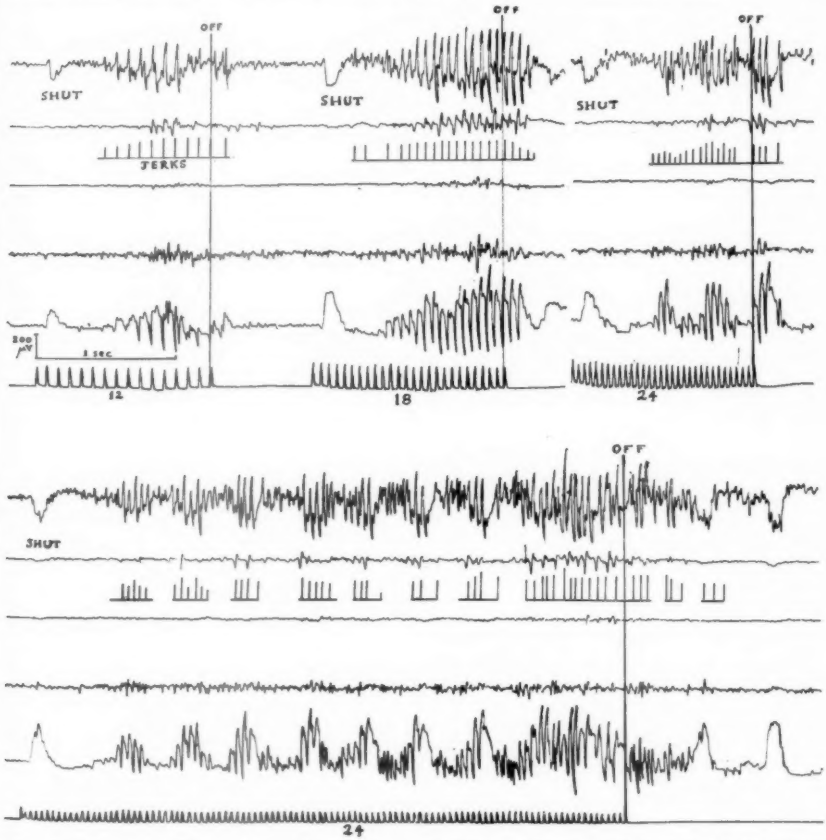


FIG. 7.—Frontal spikes and myoclonic jerks evoked by flicker at 12, 18 and 24 f/s in woman aged 42 with history of fainting for one year. Resting records normal. The spikes and jerks follow the flash frequency at multiples of six up to 18 f/s, but at 24 f/s they are grouped on the positive half-cycle of a slow wave at 2·5 c/s. The slow rise and after-discharge are characteristic. Electrodes as in Fig. 3.

phenomenon does not seem to occur in those patients who respond to flicker with wave-and-spike. In contrast also is the preservation of consciousness and absence of intense discomfort—the jerking itself is usually unwelcome to the patient, but only as an interference with proper control. It is important to realize that spikes and jerks can be evoked in any subject with the assistance of Metrazol and that this type of evoked disturbance has appeared in many patients who have been confidently described by clinicians as "hysterics". The frequency of flicker required for the myoclonic response is usually in the 8 to 13 f/s band or multiples of this. In some subjects—not necessarily regarded as true epileptics—the myoclonic response can be converted into an "organic" focal parieto-occipital sharp-and-slow wave by use of a feedback trigger driven from an alpha component; in such cases it can be seen that the slow component of the discharge suppresses the spikes and prevents the subcortical break-through at each flash.

The fourth type of evoked abnormality is the *grand-mal* seizure pattern and its usual clinical accompaniments (Fig. 8). In two patients referred only for disorders of behaviour,

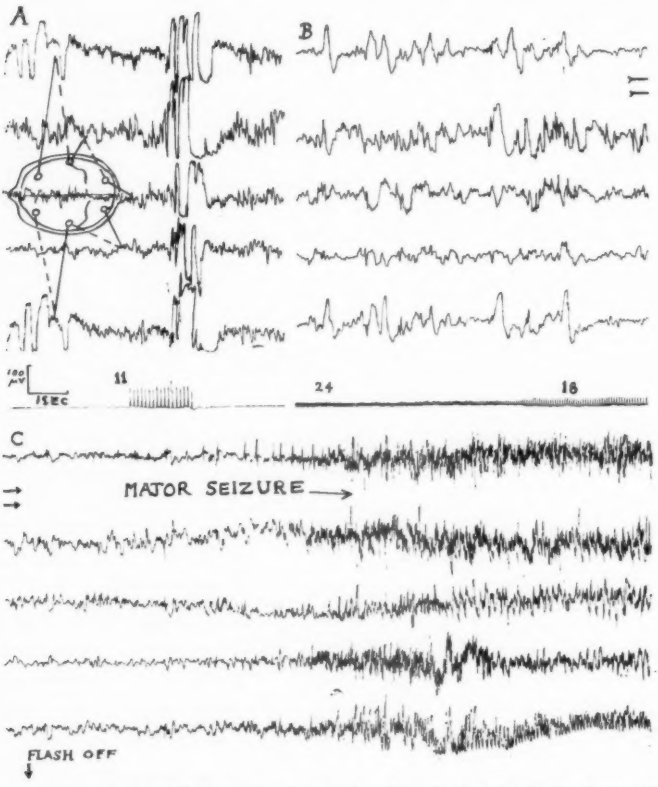


FIG. 8.—Evocation by flicker. A. Wave-and-spike. B. "Dysrhythmia." C. Major seizure in boy aged 16 with history of two fainting attacks during last three years. Resting records abnormal but not diagnostic. Electrodes as in Fig. 3.

major seizures have been precipitated by flicker at about 18 f/s; in both these, careful enquiry after the examination has revealed a history of "fainting".

From this brief catalogue it will be realized that the variety of evoked abnormalities is very great; time and space do not permit consideration of the many intriguing details which seem to form a scaffolding for the growing physiological fabric. Perhaps the most important single fact from the clinical point of view is that several of the various forms of evoked abnormality can merge one into another—several patients show a crescendo of dysrhythmia leading to wave-and-spike and culminating in a *grand-mal* seizure (Fig. 8).

As a physiologist I cannot feel content with the nomenclature and sub-classification of the epilepsies—nor even with the term itself. Practically diagnostic patterns—and clinical attacks—can be evoked in about 2% of apparently normal persons and about 5% of unstable or psychopathic ones—a tendency to diffusion and hypersynchrony seems inseparable from the elaborate plasticity of the primate nervous system.

There is still much to learn about these effects; their study in many centres is essential if we are to avoid parochial, temporary and eccentric interpretations.

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Dr. R. Sessions Hodge (Neuro-Psychiatric Department, Musgrove Park Hospital, Taunton): *Photic stimulation by multi-flash as a diagnostic measure in cerebral dysrhythmia.*—Of the numerous methods now in use for the "activation" of the human electroencephalographic record, photic stimulation has attracted us for a variety of reasons. Chief among these are:

(1) This form of stimulation is easy to produce.
(2) The patient experiences minimal discomfort.
(3) The brain stimulated is in its "normal" everyday condition and receives only physiological stimuli.
(4) The method seems to afford considerable scope for obtaining information as to the processes occurring within the central nervous system, of which the EEG is an aspect of the concomitant electrical activity.

At first we used photic stimulation as described by Walter, Dovey and Shipton in 1946, the light source being a Scophony high-power stroboscope. From this we proceeded to consider means whereby the number of cases giving positive results, of use in diagnosis, might be increased.

From an analogy with electronic calculating machines and similar devices, there arose the idea that the brain too might be "jammed" and its functioning upset if information—or stimuli—could be fed to it in such a way as to cause particular kinds of interaction between local circuits. Consideration of this soon suggested sensory stimuli as the most obvious means of achieving this and it was decided to extend the form of photic stimulation used, since this, among other things, would allow comparison with records already obtained with single-flash stimulation.

The device used consisted of four lamps, each controlled by a separate oscillator and hence capable of operation at independent flash frequencies. In the first trial model—used with all cases discussed here—gas discharge lamps were used having a spectrum covering all visible light but with a peak in the blue. These were variable in flash frequency from 0·5–30 cycles per second. The brightness of each lamp remained unaltered and crude variations of the phase of stimuli were obtained by momentary alterations in frequency.

The results obtained by this device were by no means discouraging and from the many cases seen a few examples may be selected.

Case I.—O. P., female, aged 46, referred after motor-cycle accident in which she suffered cerebral concussion. EEG, resting and during hypernœa, showed low amplitude record with asymmetrical alpha activity at 10 c.p.s. R>L. Very low amplitude irregular slow activity could be seen on the left side. Photic stimulation with single lamp gave little or no result. Multi-channel photic stimulation immediately gave rise to slow activity—chiefly in the theta band—in all areas, and the effect increased with exposure to stimulation until quite large, paroxysmal delta bursts were seen in all regions. This activity disappeared with cessation of photic stimulation and reappeared on its resumption.

Enquiry elicited the information that this patient was in fact subject to migraine and had been receiving treatment for this from her doctor for some years prior to the EEG examination. [Record demonstrated at Meeting.]

Case II.—B. J., male, aged 7 years. This boy was admitted for the treatment of extremely frequent *petit-mal* attacks. These attacks could be precipitated by hypernœa but photic stimulation with a single lamp, tried on numerous occasions, had always failed to elicit a fit. Multi-channel photic stimulation succeeded in producing two attacks, each of some 30 seconds' duration, on the

first occasion it was used. The occurrence of the "fit" appeared to coincide with particular harmonically (or near-harmonically) related flash frequencies. [Record demonstrated.]

Mention was made in the first case of apparent increase in effectiveness of stimulation with increased duration. Numerous other cases have been seen, showing similar and related phenomena. This apparent facilitation is seen in the two following cases:

Case III.—J. C., male, aged 7 years. Complained of "fits", ? following middle-ear disease. EEG record shows diffuse polyrhythmic slow activity with some slow spikes in right temporal area. Hyperpnœa has no marked effect other than some augmentation of the slower frequencies. Single-flash photic stimulation makes little or no difference to the record. Multi-channel stimulation quickly produces paroxysmal delta bursts and occasional "spike-and-wave" episodes. After exposure to multi-flash similar events could be elicited by single-flash stimulation.

Case IV.—G. K., female, aged 9 years. Epileptic controlled on drugs. Generalized cerebral dysrhythmia but non-specific. Little change seen after hyperpnœa or single-channel photic stimulation. Multi-channel stimulation makes little difference for the first 50 seconds but with increasing duration brings up large delta bursts and finally frequent paroxysmal delta activity and "spike-and-wave" episodes accompanied by myoclonic jerks.

Subjective experiences.—Patients, as a whole, appeared to find multi-channel photic stimulation less disturbing than single-channel and certain common subjective features emerged.

Generally speaking less intense visual sensations of colour were observed and patterns—often marked with single-channel stimulation—seemed less definite.

Rather less complaints of dizziness, "squeamishness" and floating sensations were experienced, but responses characterized by feelings of annoyance seemed rather more frequent than was the case with single-channel stimulation.

Inhibitory effect.—Since the technique of multi-channel stimulation appeared capable of bringing about an organization of cerebral activity corresponding to some abnormal event, it seemed possible that spontaneously occurring abnormalities might in some cases be abolished or reduced by de-synchronization of the rhythms composing them.

Comparatively few patients suitable for this form of investigation have, so far, been seen. A case is to hand, however, in which very frequent, spontaneous "spike-and-wave" episodes are greatly reduced during multi-channel photic stimulation and in others showing marked delta and theta abnormalities it has been possible to find flash combinations at which the record becomes much more nearly normal in appearance.

Possible modes of action.—It is, at present, impossible to say anything definite about the mode of action of multi-channel photic stimulation, as the process appears complex and it is possible that different mechanisms predominate in different cases. However, it may be permissible to venture a few speculations, in the knowledge that these are at best but crude and grossly over-simplified suggestions as to the cerebral processes underlying the abnormalities observed in those cases responsive to this type of stimulation.

In many—but not all—cases showing marked responses, the components seen on frequency analysis of the abnormalities are present in the unstimulated record. It is tempting to regard the chief factor here as a synchronization by the differing flash frequencies of the existing cerebral rhythms. If this were so, the role of each lamp would be to lock to it that activity at its particular flash frequency. It might then be possible by shifting the phase of the lamp flash frequencies with respect to each other to shift that of the cerebral rhythms in the same way and so achieve a configuration corresponding to the particular abnormality observed. The de-synchronization effect reported above might be explained in this way.

A further possibility is that during multi-channel stimulation a particular pulse pattern—a frequency modulation effect—is attained, which corresponds to a series of critical time-intervals in the systems involved in the progress of the impulse. It may well be that this is not merely frequency modulation but a combination of that with amplitude modulation. If this should be the case, then it seems that although the correct pattern might be produced on a single lamp (model displayed at meeting) the chances of finding it are very much greater if multi-channel stimulation is used.

If the abnormal event, once started, may be in any way regarded as a self-sustaining process—or, at any rate, one with appreciable decrement—then, presumably, random stimulation must eventually cause its appearance. It is possible that this quality of randomness may be of importance in its application to the cerebral matrix and in the appearance of apparently isolated cerebral disturbances.

Work at present in progress suggests that all these and other factors, many of which are undergoing further investigation, are of importance in photic stimulation and that the field of controlled sensory stimulation may provide a safe, simple and effective means of improving the EEG diagnosis of epilepsy and allied conditions of cerebral dysrhythmia.

Dr. S. L. Last (Runwell Hospital, Wickford, Essex): I propose to discuss the use of some of the drugs which have been employed, but I am afraid that the majority of these have to be dismissed as not very satisfactory for our problem. Insulin has been found, by most of those who have tried it, too unspecific. The same applies to the water-pitressin test. It is true that Gellhorn and Ballin (1946) have given favourable reports of it, but other authors, who have employed it on a larger scale, have found that a number of their controls produce slow EEG activity which was very much like that produced in epileptics. Better results appear to have come from the use of hypnotics. This is a technique which has not been especially popular in the EEG centres in this country, but the Gibbs (1947) school in the United States have repeatedly reported the excellent diagnostic results obtained from EEGs during sleep. They recorded during natural sleep or during sleep induced by drugs; they felt convinced that the hypnotic drugs employed are not themselves causing changes, but these are brought out by the sleep which they think is identical with so-called natural sleep. Their work has been confirmed, particularly by French workers.

However, the main line of attack has been with Leptazol. It was introduced as a diagnostic help before the EEG era. I believe the first attempts were made in Germany and it was again taken up towards the end of the last war, both on this side of the Atlantic and in the United States. The results of using it without EEG have been disappointing in that it has not been sufficiently specific. One had hoped that it would be possible to find a dose so low that it would hardly ever produce an epileptic seizure in a normal, but sufficiently high to provoke an epileptic fit in the majority of epileptic patients, and the dose with which most people have worked has been round about 2 or 3 c.c. of the 10% solution. Unfortunately, the overlap of the two types of cases, the normals and epileptics, has been too large to be disregarded; in other words, there are quite a few epileptics who are more or less resistant to the administration of Leptazol and a number of normals who will go off into a fit on very small doses. It is more successful if employed in conjunction with the EEG although here, too, it has its limitations.

There are two main ways of using it. It has either been given as a rapid injection as in the treatment of psychoses, or as a slow injection, with or without the addition of other stimuli, like photic stimulation or overbreathing. And, again, one has to distinguish between the object of achieving the diagnosis epilepsy or not epilepsy, and the attempts to find out in cases of known epilepsy where the focus is or what type of fit the patient has.

The rapid injection has been used by Kaufman and others in Baltimore (1947), and by Cure and his co-workers (1948) in Montreal, and I reported on some results three years ago at a meeting of the Royal Medico-Psychological Association. Diagnostically it compares unfavourably with the slow injection, but it gave me results which were interesting in an unexpected way. Table I shows the 25 patients divided into those who had a normal

TABLE I.—RESPONSE TO INJECTION OF LEPTAZOL

	Number of cases having no fit	Number of cases having convulsive response	Total
Number of cases with normal EEG	4	0	4
Number of cases with doubtful EEG	4	0	4
Number of cases with abnormal EEG	8	9 (2 twitchings only)	17
Total	16	9	25

resting EEG, those whose EEG was doubtful and those whose EEG was frankly abnormal. Neither in those with a normal, nor in those with a doubtful EEG, could clinical epileptic phenomena be provoked by 2 c.c. of the 10% solution of Leptazol, but in 9 out of my 17 patients with abnormal EEGs this small dose produced fits or severe twitches. From a diagnostic point of view this must be classed as a failure as the Leptazol brings confirmation in the cases who are already known to have abnormal EEGs but not in those in whom evidence would be welcome; but it seems noteworthy that the epileptics with an abnormal EEG showed a greater liability to respond with a convulsion to a small dose of Leptazol than those whose EEG was normal. This has been confirmed by other authors and in conjunction with the findings of others one comes to the conclusion that it is the cases whose epilepsy is not due to localized cortical disturbances who are more likely to respond to the smallest doses of Leptazol, in other words it is the group of idiopathic epilepsy.

A somewhat greater success has been the slower injection. In Los Angeles Ziskind and his collaborators (1947) have determined the minimum dose required to provoke paroxysmal EEG abnormalities by slow injection, and after standardizing their slow injection technique in animals they have applied it to humans and have found that less than 2·5 c.c. of the

10% solution would provoke paroxysmal abnormalities in the EEGs of 72% of epileptics. On the other hand more than 82% of the non-epileptics require a dose larger than 2·5 c.c. These figures correspond quite well to those published by the Montreal workers who found with their technique of slow injection that they got an abnormal EEG response in 80% of epileptics and in 15% of normals. Such figures sound quite satisfactory but the findings can hardly be regarded as a real help when dealing with the diagnostic problem of one case because they mean that one out of seven normals may show what is considered an abnormal response.

Much more useful appear to be the findings which these workers have made and which confirm those of Kaufman and Earl Walker in focal lesions, particularly of the cortex. Here it has been possible to evoke abnormal discharges by continued slow injection in

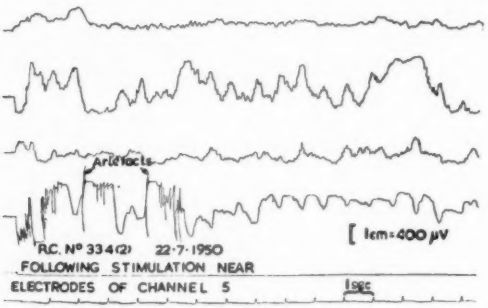

FIG. 1.—Response from normal cortex to electrical stimulation.

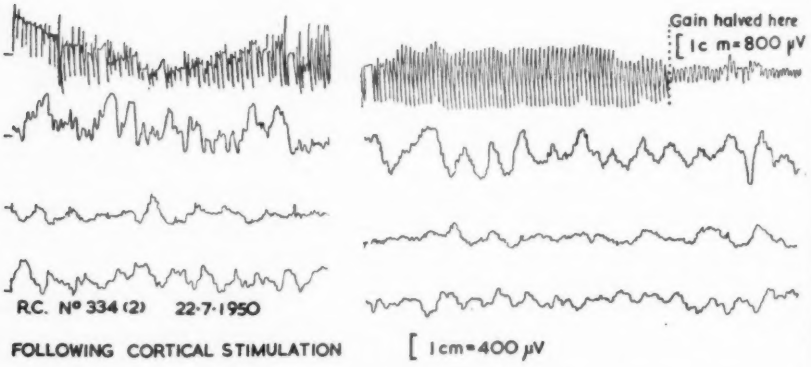

FIG. 2.—Response from "trigger area" to cortical stimulation. The record was interrupted for two seconds.

cases of focal lesions and the material of these two centres presents very convincing evidence that one can localize circumscribed lesions and particularly scars by this method. In some cases the evidence will rely on the EEG, that is one will find spike or slow wave discharges starting in a certain area. In other cases one can see a focal fit arise, the course of which will provide the evidence necessary for the location of the lesion. The technique employed is simple. All that is required is a slow injection of a dilute solution. 2 to 5% is the dilution recommended and the rate of injection has been kept at about 1 to 2 c.c. per minute. It is this use of Leptazol which seems to constitute the greatest advance in the use of drugs in conjunction with the EEG.

The method of cortical stimulation is described particularly by Earl Walker (1949). It is used during operation where an electrocorticogram is being taken, the electrodes being applied to the cortex itself. The cortex is then stimulated electrically. If the neighbourhood of a scar in a traumatic epileptic is explored in such a manner one can find that certain areas respond in a much more violent manner than others. There will be circumscribed regions,

which on stimulation give rise to prolonged high voltage discharges. Such areas can be regarded as trigger areas and while they are responsible for the "firing off" of epileptic seizures, their removal is said to abolish or reduce the fits in traumatic epilepsy.

Figs 1 and 2 demonstrate an electrocorticogram recorded during an operation performed by Mr. D. W. C. Northfield. Fig. 1 shows the response of a normal and Fig. 2 of a "trigger area".

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Dr. John T. Hutchinson (Department of Clinical Neurophysiology. Institute of Psychiatry, Maudsley Hospital, London): I wish to describe the problems involved in the EEG diagnosis of epilepsy, and the various methods used to provoke epileptiform changes in patients. These I shall contrast with a description of my experience with subconvulsive doses of Metrazol (Cardiazol) as a provocative agent. It is of interest that the early medical writers were just as intrigued by the diagnostic problem of latent epilepsy as we are to-day. Indeed, many of the provocative methods they described are used now with very little degree of refinement. Apuleius, in his Apologia, described the effect of exposing susceptible individuals to the sun's rays which were broken up by the whirring spokes of a potter's wheel; a method which we now reproduce by electronic means in the form of a flickering light from a stroboscope (Temkin, 1945).

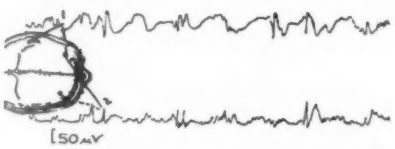

FIG. 1.—Frontal spike focus seen during insulin hypoglycæmia.

Until recently, indeed, until the more widespread use of electroencephalography, the water-pitressin test was considered to be a worth-while diagnostic method, although those who used it made little mention of its unpleasant effects. In 1943, Garland, writing on the use of the water-pitressin test, dismissed the value of overbreathing, Metrazol and ethylchloride as being ineffective, and stressed the value of the hydration technique. He then described a series of 44 patients who were definitely epileptic, in 17 of whom epileptic seizures were produced; a further group of 32 of more doubtful history is described, in 12 of whom epilepsy was diagnosed by this method. In 1947, Cohn described his work with the water-pitressin test used in conjunction with electroencephalographic examination. He was not impressed by the method since he considered that water intoxication does lead to changes in the electroencephalogram in the majority of individuals, but this response is not specifically epileptic, and, apart from that, he found patients having *grand mal* seizures who showed no EEG disturbance during the period of water intoxication. A further contraindication was the risk of death occurring during the test.

But these tests are not without their clinical significance, and in 1943 Hill and Sargant described the case of a young man who murdered his mother after consuming five pints of beer. In this case, the patient's metabolic state at the time of the crime was reproduced in the laboratory during an EEG examination in association with other metabolic tests. It was clearly shown that the association of a positive fluid balance and a low blood sugar tended to produce EEG abnormalities. Hypoglycæmia has been used in other connexions to bring out cortical instability. Lennox and Gibbs have described its use (1938), and again Hill has done extensive work in this connexion (1948), bringing out the spike-and-sharp-wave activity in the EEG records of catatonic schizophrenics.

Fig. 1 is from the electroencephalographic record of a patient suffering from post-traumatic epilepsy, in whom a focus of epileptic activity has been clearly demonstrated by the method of injecting insulin. This patient is a young man, who, some years ago, sustained a frontal head injury and had a plate put in to cover the bony defect in his skull. More

recently, he has suffered from a psychiatric illness which was diagnosed as schizophrenia, and he was considered suitable for insulin shock treatment. He began to have seizures in insulin coma, and an EEG was carried out one morning during treatment. It is of interest that he recovered very rapidly following one or two such seizures. In the series of cases which I shall describe, use was made of this tendency for abnormalities to be facilitated by a low blood sugar. All of my patients were examined in the fasting state.

It is well known that many epileptics have their attacks during sleep. The Gibbs (1947) claim to have observed epileptic changes during sleep in a high proportion of the patients examined by them. They examined 500 epileptics and stated that 82% showed seizure

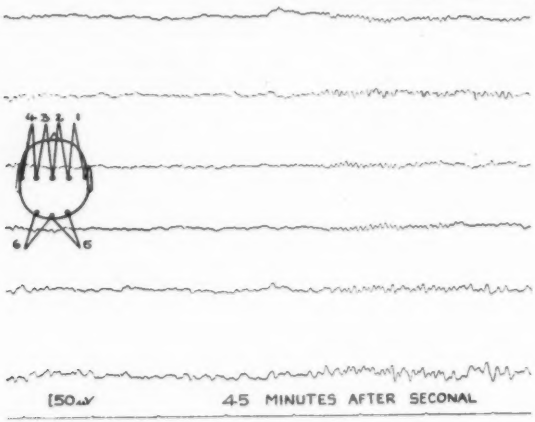

FIG. 2.—EEG appearances of normal sleep after Seconal.

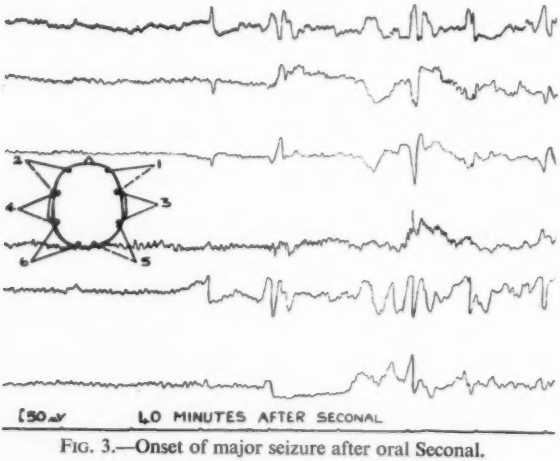

FIG. 3.—Onset of major seizure after oral Seconal.

discharges during sleep, and only 36% showed such changes when awake. Our work at the Maudsley Hospital has been confined to borderline cases whose resting EEG showed no epileptiform abnormality. Sleep has been induced in them by the use of Seconal following the methods described by the Gibbs (1949) and Wyke (1950). A dose of 3 grains was given to an adult, and this dose was repeated if evidence of barbiturate activity did not appear in the record within forty minutes. It is difficult to understand why this technique should produce epileptiform changes, and one can only mention conjectural reasons. There is no doubt that a drug such as Seconal rapidly produces fast activity in the region of 14 cycles per second. This is followed by sleep in which high amplitude slow waves alternate with electrical silence. (Fig. 2 illustrates the appearance of barbiturate fast

activity.) This combination of fast and slow high voltage activity is a caricature of the spike and wave associated with idiopathic epilepsy, and it may be that in susceptible individuals the caricature serves to evoke the latent abnormality. In any event, there is an alteration in the control of cerebral function, which may facilitate the appearance of latent epileptic phenomena. Fig. 3 is part of the record of a patient in whom status epilepticus was accidentally produced by the administration of Seconal. This was a mentally defective girl, aged 23. The only relevant history was the fact that she had had two previous fits which had occurred outside the mental defective colony from which she came, and there was also said to be a family history of epilepsy. She proved to be extremely tense and apprehensive, and the first record taken was completely valueless since it was dominated by the presence of muscle artefacts and no cortical activity could be seen. Therefore, it was arranged to repeat the examination, and she was given 3 grains of Seconal beforehand to allay her anxiety and to enable an artefact-free record to be obtained. It was interesting to observe that exactly forty minutes after taking 3 grains of Seconal by mouth, she began to have fits which were controlled only with difficulty by the administration of a large dose of Gardenal. In only one other epileptic did I have the opportunity of observing a seizure following the administration of Seconal. This patient was having almost daily attacks of psychomotor epilepsy, and it may well have been purely a coincidence that such an attack occurred after taking this drug. Seconal is certainly not a potent epileptogenic agent since, of 60 borderline epileptics examined by this method, in no case did the EEG abnormalities of epilepsy appear.

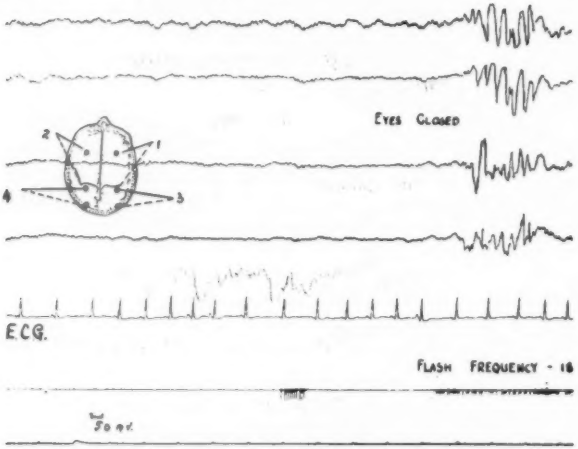

FIG. 4.—Atypical spike and wave discharge induced by photic stimulation at 18 flashes per second.

Delay has claimed recently that scopochloralose is of use as an epileptogenic agent (Delay and Verdeaux, 1949). It was tried out in a few patients here. The first two showed no response whatsoever, and the third showed no response during EEG examination, but four hours later he developed an unusual clinical picture characterized by confusion, disorientation, pallor, a pulse-rate of 40 and a marked fall in blood pressure. This state responded to intravenous Methedrine. No further investigations with scopochloralose have been made.

The use of sound as a means of provoking cerebral dysrhythmia has interested many people, and the use of rhythmical music by primitive native tribes to produce mass excitement would suggest that there is a closely allied field of study yet awaiting investigation. The cases of musicogenic epilepsy described by Shaw and Hill (1947) and also by Critchley (1937) are really clinical rarities. Gastaut has recently assessed the value of auditory stimulation in a group of subjects who showed positive epileptic discharges on photic stimulation, but the results proved disappointing (Gastaut and Pirovano, 1949).

Intermittent photic stimulation has become a popular method of inducing epileptiform abnormalities in the EEG. The technique used by us has been that described by Grey Walter in his recent Maudsley Lecture (Walter, 1950). Frequencies of between 15 and 18 per second were used, combined with eye closure. Fig. 4 is that of a girl who suffered from epileptic attacks which were associated with autonomic phenomena—rapid alterations in

the pulse-rate, pallor of the skin and dilatation of the pupils. The record shows clearly the association between eye closure, photic stimulation and an atypical spike and wave discharge from the cortex. Fig. 5 shows very much the same phenomenon. This record is that of a man who suffered from *grand-mal* seizures, and also from epileptic equivalents, in which he carried out purposeful behaviour, such as stealing motor cars and attacking people. Fig. 6 is taken from the record of a patient who was suffering from Unverricht's myoclonus epilepsy. The effect of stimuli at 14 flashes per second was to produce rhythmical

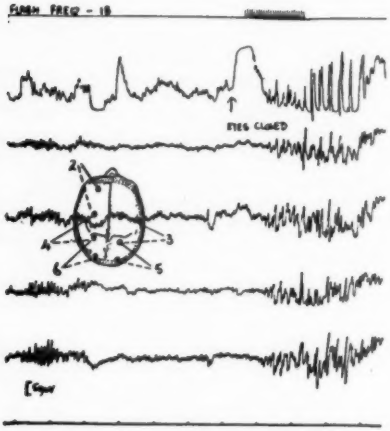

FIG. 5.—Spike discharge evoked by the combination of eye closure and photic stimuli at 18 flashes per second.

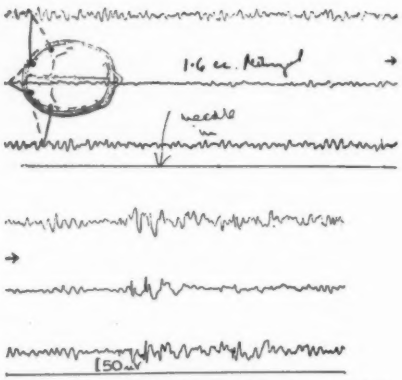

FIG. 7.—Bilaterally synchronous atypical spike and wave discharge produced by the injection of 1·6 c.c. 10% Cardiazol.

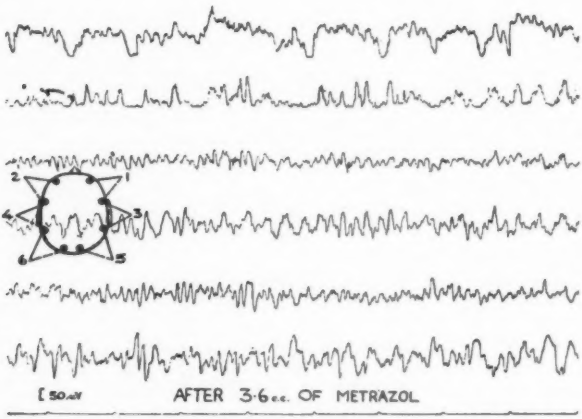

FIG. 8.—Onset of major seizure discharge in left hemisphere following injection of 3·6 c.c. 10% Cardiazol.

jerking movements. The spikes which can be seen are at 3½ per second, obviously a frequency which bears a numerical relationship to that of the light stimulus. The lower half of the record shows the effect of tridione therapy which serves to inhibit the response to photic stimulation.

I must emphasize that the resting records of each of these 3 patients showed clear abnormalities, and one could have made a diagnosis of epilepsy without having recourse to any of the provocative approaches. I investigated over 100 patients whose resting records showed no epileptic phenomena, and in no case did I succeed in eliciting epileptic discharges.

The chief method of provocation which I have used has been the injection of divided doses of Cardiazol without photic stimulation. This method has been described by Jasper and his co-workers (Cure *et al.*, 1948), who claim that in 100% of patients suffering from cryptogenic epilepsy, a positive diagnosis can be made by the use of this method, which is, briefly, as follows: A 10% solution of Cardiazol is used. 5 c.c. of the solution is drawn up into a graduated syringe. The solution is injected intravenously, and the dosage depends

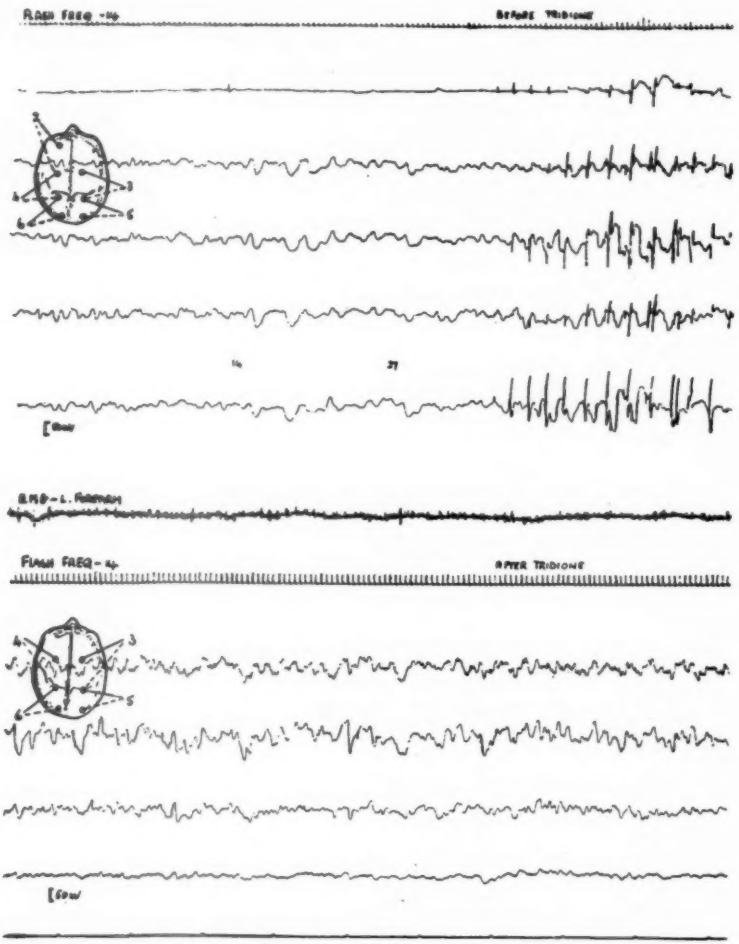

FIG. 6.—Unverricht's myoclonus epilepsy. Upper half shows spike discharge on photic stimulation. Lower half shows effect of Tridione in inhibiting such a discharge.

on the patient's body-weight. It is 0·01 c.c. per lb. (0·022 c.c. per kg.) body-weight initially, and 0·005 c.c. per lb. (0·011 c.c. per kg.) body-weight at 30-second intervals until approximately 4 c.c. have been injected, or until abnormalities appear. Thus, if the patient weighs 140 lb. (63·64 kg.), the initial injection is 1·4 c.c. and 0·7 c.c. at subsequent 30-second intervals. During the injection, a careful watch is kept on the record. As soon as abnormalities appear, the needle is withdrawn. A major seizure may be provoked by this method. Therefore, it is important to ensure that the patient is fasting, that dentures are removed, that a mouth gag is to hand and that the patient is not suffering from any medical condition in which a seizure would be harmful. The following examples illustrate the method: Fig. 7

shows the record of a patient who had nocturnal attacks in which he saw hundreds of dead soldiers walking past him. When he wakened in the morning, he often found that he had bitten his tongue and had been incontinent. His resting EEG was normal, but the injection of 1·6 c.c. of Cardiazol was sufficient to produce spikes and slow waves. Fig. 8 is from the record of a patient who suffered from fits which were initiated by jerking movements of the right hand and forearm. The tracing shows the initiation of a seizure discharge in the left hemisphere. Fig. 9 is from the record of a patient who had had only three attacks of a rather unusual nature. These were nocturnal, and were always initiated by an aura in which he experienced a powerful impulse to defæcate. It required the injection of 4 c.c. of 10% Cardiazol in divided doses to produce the paroxysmal discharge of spike-and-wave activity which continued for three to four minutes before disappearing. The patient was unaware of any associated mental disturbance.

Using the Cardiazol technique alone, 100 patients have been examined. These were patients whose clinical histories suggested a diagnosis of epilepsy, but ordinary EEG examinations showed no epileptiform abnormality. 43 (43%) of these showed a positive response to the injection of Cardiazol in divided doses. A positive response is considered to be spike-and-wave, spikes or high voltage slow waves following injection of up to 4 c.c. of 10% Cardiazol.

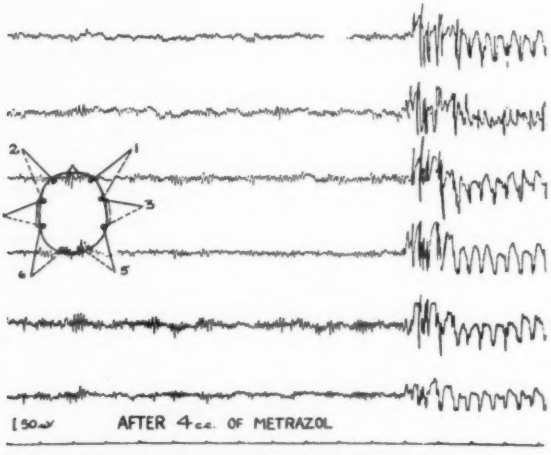

FIG. 9.—Atypical spike and wave discharge produced by the injection of 4 c.c. 10% Cardiazol.

There were thus 57 patients (57%) who showed no abnormality. On a further survey of the clinical material, it was considered that only 6 of these 57 cases could be considered to be epileptics on clinical grounds. A further review of the group of 43 patients which responded to the stimulus showed that it contained 18 patients suffering from psychomotor epilepsy, 10 who had major epilepsy characterized by *grand mal* seizures, 2 cases of post-traumatic epilepsy, 2 patients who had migraine, 1 post-encephalitic Parkinsonism and 10 patients suffering from conversion hysteria.

There were thus 36 true epileptic patients in the total series of 100, of whom 30 (83%) gave a positive response to the test, whereas of 64 non-epileptics only 13 (20·3%) gave positive results.

In analysing these results further, it was seen that 30 (69·8%) of the 43 who had a positive response showed a spike-and-wave discharge, 8 (18·6%) showed high amplitude slow waves, and 5 (11·6%) showed spike activity only. These wave forms were shared by all the clinical groups described above, indeed, 8 of the 10 hysterics showed spike-and-wave, only 2 showing a slow wave discharge.

A further analysis was made of the resting records of the patients in an attempt to see whether any fresh indication could be given by them of the type of response that would ultimately develop on exposure to Cardiazol. Of the 43 patients who gave a positive response, only 4 had resting records which showed fast and slow dysrhythmia, only 2 showed predominantly fast activity, 25 showed predominantly slow activity and 12 were considered to be normal.

In 57 subjects who failed to respond, only 8 had fast and slow activity, 4 had predominantly fast activity alone, 23 were dominated by slow activity and 22 had normal records.

These comparisons would suggest that the presence of slow waves in the resting record favours a positive response to Cardiazol. This contention is supported by the examination of the resting records of 36 true epileptics (Table I).

TABLE I.—ANALYSIS OF RESTING RECORDS OF 36 TRUE EPILEPTICS

	EEG				
Metrazol	Fast and Slow	Slow	Fast	Normal	Total
Positive response ..	4	22	2	2	30
Negative response ..	0	5	1	0	6
					36

The average age of the 57 patients was 31·61 years, and the average amount of Cardiazol injected in each case was 4 c.c. The average age of the 43 who gave a positive response was 29·95 years. The average amount of Cardiazol injected in this (i.e. the positive) group was 3·17 c.c. S.D. = 0·97.

The coefficients of correlation between Cardiazol dosage and age of patient, and between Cardiazol dosage and weight of patient did not show any significant relationships (Table II).

TABLE II

Mean dosage of Cardiazol = 3·17 c.c.
α = 0·97

Mean age of 43 patients = 29·95 years
α = 10·83

Mean body-weight of 43 patients = 133·48 lb.
α = 25·05

Coefficient of correlation Age/Dosage r = 0·26.
" " " Wt./Dosage r = 0·003

CONCLUSION

In comparison with other methods of activation the use of divided doses of Cardiazol is the most valuable in the diagnosis of cryptogenic epilepsy. Other writers have described the Metrazol threshold in control subjects, and have considered that it is beyond 4 c.c. In the series which I have described, it is seen that apart from being an aid to the diagnosis of epilepsy, it may accentuate the tendency to convulse which every individual possesses. It is possible that there is a normal distribution curve of this tendency to have fits, and that subjects who share the lower end of the curve with the epileptics may show a positive response to this test. It is of interest that 10 patients suffering from conversion hysteria showed a positive response. This is obviously a matter which requires further elucidation.

I am indebted to Dr. Denis Hill, at whose suggestion this work was begun. I also wish to thank Dr. D. A. Pond for his advice and criticism.

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Dr. Denis Hill (Institute of Psychiatry, London) said that these new developments in the study of the epilepsies were of the greatest theoretical interest and might well lead to a better understanding both of the essential mechanism of the epileptic discharge and of the many exciting causes of it. However, not only patients with undoubted idiopathic epilepsy, but also others with seizures consequent upon disease or damage to the brain could be induced to have a clinical seizure or to show electroencephalographic evidence of epileptic discharge by these procedures. In some cases, irrespective of the diagnosis, EEG discharges follow after any or all of these procedures, in others the EEG only changes with some techniques, not others. Yet with clinical electroencephalography, recording through the intact skull, the location of epileptogenic cortical foci in the neighbourhood of atrophic lesions had not been greatly assisted by these techniques. Those who had the opportunity of recording from the exposed brain claimed much better results, particularly with the use of Metrazol, and the subconvulsive dose of this drug could be used successfully to locate the epileptogenic cortical focus. Unfortunately there was as yet no drug and no technique which could easily differentiate an epilepsy in which the exciting focus was in the cortex, from one in which the discharge immediately involved the diffuse thalamocortical mechanisms. At the present time the speaker thought that Metrazol and induced hypoglycæmia were the best techniques for exciting the local cortical focus, whereas flickering light certainly facilitated the thalamocortical mechanism. But Metrazol in larger doses also did this. Flickering light was rather disappointing. While the majority of patients in whom the EEG already spontaneously showed evidence of epilepsy had their subclinical epilepsy greatly facilitated by the method, he thought it was true that less than 5% of epileptics with normal EEG records gave positive results. The practical value was therefore reduced. Nevertheless in some patients whom he had observed repeatedly by this method, the response to the light was found to vary from day to day and a positive result might be obtained sometimes on the second or third attempt.

All these methods, hydration, hypoglycæmia, barbiturate sedation, Metrazol and the photic techniques, only served once more to widen our ideas about epilepsy which was no longer a disease or even a syndrome. By the use of these methods not only idiopathic epileptics, but also many patients with brain tumour, damage or degeneration, catatonic schizophrenics, psychotic patients and others with episodic behaviour disorders of all types, even some hysterics as had been shown, produce EEG discharges of the "epileptic" type. In many of these patients the phenomena vary with time, sometimes being present, sometimes absent. There were undoubtedly many as yet unknown factors determining whether a patient actually shows clinical or subclinical evidence of the "epileptic" brain disorder. At the present time the decision whether any given patient's attacks or symptoms were the immediate and direct result of this disorder, must remain a clinical decision which must be made on clinical evidence, whatever the EEG result might be when one of these activation methods was used.

Section of Neurology

President—W. Russell Brain, D.M., P.R.C.P.

[*November* 2, 1950]

Meeting at the National Hospital, Queen Square, London, W.C.1

Cervical Hæmatomyelia Causing Profound Tetraplegia and Loss of Sensation in a Patient with Congenital Heart Disease. Recovery after Operation.—Diana J. K. Beck, F.R.C.S.

C. E., a married woman aged 38, was admitted to the Middlesex Hospital on September 18, 1950, on account of progressive weakness and numbness.

History.—In 1941 she was in the bombing of Coventry and whilst moving furniture experienced sharp pain in the lower back; this was ascribed to spondylitis and relieved by bed rest and a plaster jacket.

Hysterectomy for menorrhagia in March 1947 was followed by cystitis. In August 1947 she began to have frequent attacks of stabbing pain in the left side of her chest, radiating down the inner side of her left arm and up the left side of her neck. There was less severe pain in the back and down the back of the left leg. The next two years were spent mostly in bed because of irregular fever, profuse sweats, weakness, breathlessness and occasional ill-defined pain in her chest.

Investigations at Folkestone Hospital, 1947 (Dr. F. H. Fletcher): Apical and pulmonary systolic murmurs. Blood tests negative. E.S.R. 4/100 (Wintrobe) on admission and 24/100 on discharge when patient was afebrile.

Investigations at Pembury Hospital, early 1948 (Dr. H. M. Miller): Negative apart from heavily infected urine which responded to sulphatherapy.

She was first admitted to the Middlesex Hospital in late 1949 (Dr. G. E. S. Ward) and was regarded as having congenital heart disease (? patent foramen ovale) with a superadded neurocirculatory asthenia.

No more was heard of her until the time of her readmission on September 18, 1950, although during the intervening nine months she had never been up for more than five hours a day. The cardiac findings were unchanged. The cranial nerves were normal. There was increased tone in both upper limbs, which showed weakness more marked on the left than on the right. Both lower limbs showed spastic weakness. There was some sensory loss

of light touch, pin-prick and differentiation of heat and cold below the clavicles and loss of postural appreciation in fingers and toes. Tendon-jerks were increased, particularly in the lower extremities; there was ankle clonus on the left and both plantar responses were extensor.

Marked deterioration occurred within a few days. Dr. Douglas McAlpine saw her on September 22, 1950, and suspected a cervical intramedullary tumour. Lumbar puncture: Pressure 85 mm.H_2O with complete manometric block. Fluid: clear, colourless. 1 lymphocyte per c.mm., 60 mg.% protein.

X-rays showed complete hold-up at C 6 (5 c.c. myodil) (Figs. 1 and 2).

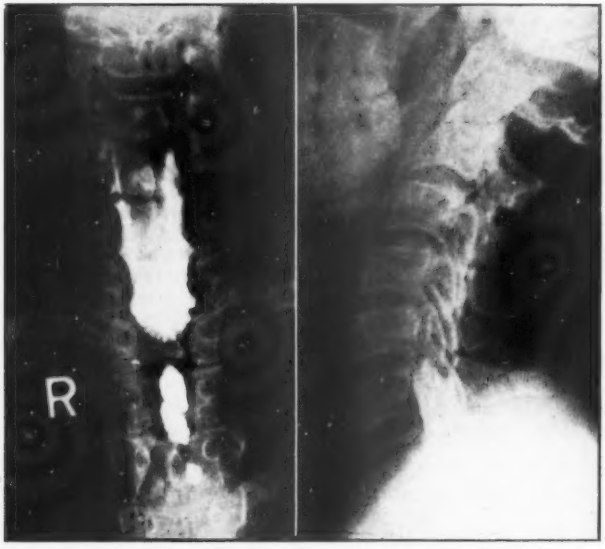


FIG. 1 (A.P. view). FIG. 2 (Lateral view).
Showing complete hold-up of myodil at C 6.

Examination.—September 23, 1950 (D. J. K. B.), immediately after myelography: Pupils: right larger than left, but both reactive. There was profound spastic weakness of all limbs with bilateral ankle clonus and bilateral extensor plantar responses. Respiration was diaphragmatic. There was complete loss of all forms of sensation below the clavicles.

Operation (September 23, 1950).—*Laminectomy C* 3, 4, 5 *and* 6. *Aspiration of hæmatomyelia of cord.* Findings: Cord tightly pressed against bone opposite C 4, 5 and 6. Bone thinner on right than on the left side. Spindle-shaped swelling of cord, 3 cm. long, of firm consistency opposite C 4, 5 and 6. Vascular pattern normal. No pulsation of cord below the upper level of the swelling. No tumour in front of cord. Arachnoid adherent over swelling. "Tumour" aspirated: 3 c.c. of blood obtained with prompt disappearance of swelling and resumption of pulsation of cord.

At the end of operation, bleeding and clotting time were normal. Platelet count, 300,000 per c.mm.

By the next morning she had a moderately good hand-grip, was moving her toes and could appreciate pin-prick all over. P.R. R. ↓ L. ↑. Within six days she was feeding herself and moving all her limbs freely. She continued to improve and was up and walking within fourteen days. She now has no abnormal neurological signs except exaggerated tendon reflexes and bilateral finger-jerks.

Comment.—There are several interesting points about this case. She is the subject of congenital heart disease (? patent foramen ovale) and had led a full life up to 1941, when she was in the bombing of Coventry. Since a hysterectomy for menorrhagia in 1947 her existence has been that of an invalid, punctuated by febrile episodes, in one of which scattered but transient petechial hæmorrhages were found in the skin. Searching investigations failed to prove subacute bacterial endocarditis.

Then during recent months there was progressive weakness and numbness of the limbs with rapid advance over four to five days, an advance accelerated by myelography, after which respiration was dependent on the diaphragm.

The finding of a hæmatomyelia at operation naturally called for the exclusion of a blood disease as the cause.

The absence of abnormal neurological signs now, makes it most unlikely that either a tumour or syringomyelia is the underlying pathology.

It seems that we are left with the assumption that the congenital defect of her heart is associated with telangiectasis of the cord.

The spastic nature of the weakness and the lack of interference with the sphincters suggest that the lesion was slowly progressive although there was shortly before operation a fulminant episode causing swelling of the cord, with increase in the motor signs and loss of all forms of sensation below that level.

I believe that it was to this patient's advantage that I failed to correlate her cardiac and spinal conditions, for knowing that a remarkable degree of recovery occurs in hæmatomyelia, I might have denied her relief by surgery and it is almost certain that she would have died without it.

Infantile Hemiplegia Treated by Hemispherectomy.—L. S. WALSH, F.R.C.S. (for WYLIE MCKISSOCK, O.B.E., M.S.).

E. P., female aged 20, a packer. Admitted to National Hospital on 31.3.50. Discharged on 3.7.50.

History.—"Epileptic fits" since she was 7 years old. Paralysis of left side of body since birth; worse for three months. Born with paralysis of left limbs. Did not walk or talk until she was 8 years. Began school at this time and continued until she was 14 years old, having completed the third form. Aged about 7 years she had chickenpox and about three months later a febrile illness which was suspected scarlet fever. She was sent to hospital and while there developed left-sided fits. These have continued and have been more frequent since January 1950. The fits start with a feeling of numbness in the left hand and this spreads to the trunk and leg. The left arm and leg become drawn up and she falls unconscious. There is tongue-biting and occasional urinary incontinence. The whole attack lasts five to eight minutes, and she has been having attacks two or three times a week; usually at night. She has also had numerous attacks of numbness of the left hand which do not progress to involve the rest of the body and which are not associated with unconsciousness.

She has been on anti-convulsive therapy of phenobarbitone and epanutin.

The weakness of the left arm has been increasing since January 1950. She has been quarrelling with her sister and parents, particularly during the past three months.

On examination.—Co-operative but of limited intelligence.

Cranial nerves.—Visual fields: on confrontation some constriction of the left visual field, particularly temporal portion. Right full. Discs normal. Some deafness of the left ear. The left arm and leg were smaller than the right. They showed moderate increase in tone and were weak, most markedly in flexion and extension of the left wrist and the fingers of the left hand, and there was marked inco-ordination.

Touch, temperature and pain normally perceived on the left side. Slight impairment of vibration sense on left, but severe impairment of position and joint sensibility, two-point discrimination and graphæsthesia. There was astereognosis on left side. Reflexes increased on the left side and left plantar response extensor.

General examination normal.

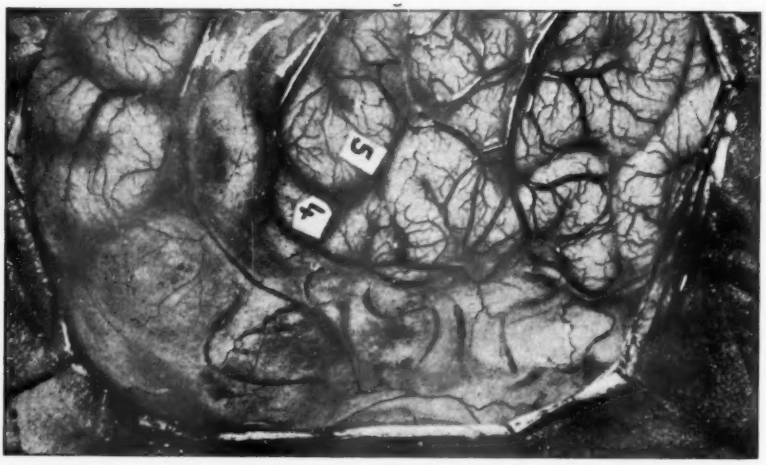
Special investigations.—Straight X-ray: Right side of skull smaller than left. E.E.G.: Alpha rhythm less evident on right with slow waves over both hemispheres. Focus of recurrent single waves which might be attenuated "sharp waves" in right occipito-temporal region. Blood W.R. negative.

12.4.50: *Air encephalogram*: Dilated right lateral ventricle with a large cyst in the right temporal region.

2.5.50: *Right common carotid arteriogram*: Anterior cerebral arteries displaced to the right—confirm the atrophy shown in encephalogram.

11.5.50: *Psychiatric report*: Disorder of behaviour of the epileptic kind.

18.5.50: *Hemispherectomy with stimulation of the cortex*, in collaboration with Dr. J. A. V. Bates who kindly supplied the photograph (Fig. 1).



L. R.

FIG. 1.—Photograph of exposed brain. The mid-line is uppermost and the anterior aspect on the right. The points 5 and 4 produced movement of the left hand on stimulation—*see* text. The cortex below and behind the sylvian fissure was grossly abnormal and in this region no recognizable cerebral tissue was seen.

Point 5: Movement of left wrist and fingers 3, 4, and 5 of left hand. These movements were followed by a generalized fit.

Point 4: Movement of left wrist.

29.5.50: *Post-operative E.E.G.* The left side is not greatly different from the pre-operative state. The right side is not devoid of activity, showing low voltage alpha rhythm and phase and distribution studies suggest that this may be arising from the stub of hemisphere which has been left.

21.6.50: *On examination* she was cheerful and co-operative and said she felt better than before operation. She had had no fits and thought that her left arm was less stiff than before operation and of more use to her.

She had a left homonymous hemianopia.

Apart from some decrease in the spasticity of her left arm and leg there was no other change noted on examination.

A recent report states that she has had no fits and is much more pleasant at home.

[*December* 7, 1950]

DISCUSSION ON PARIETAL LOBE SYNDROMES

Dr. **Macdonald Critchley** (Physician, National Hospital, London): The clinical manifestations of parietal lesions are of unusual interest and topicality. This was a happy choice for a subject of discussion in a neurological society—chiefly, perhaps, because it can be used as a text upon which to debate the present-day tendencies in our attitude towards cerebral function.

As opener, my chief difficulty is to curb my remarks within the compass of thirty minutes, and to make a choice from the very many aspects of parietal function which might be discussed. It would be easy and no doubt impressive to project an outline chart of a cerebral hemisphere and to mark with a little cross or a circle what I imagine to be the centre of a three-dimensional region of disease quite irrespective of its size or shape; further to assume that it corresponds with some such anatomical convention as, say, the supramarginal gyrus; and then lastly to try and correlate this lesion with some of the outstanding clinical features which I had happened not to have overlooked during life. It would also be comparatively easy to get led away into a discussion on cerebral dominance, or alternatively of manual preference; and to speak of major hemispheres and minor; dominant and subordinate.

It would be simple to tabulate lists of parietal signs, or even parietal syndromes, and to equate them with disease of one hemisphere or both, that is right or left side without discrimination: or specifically with disease of the dominant or of the subordinate hemisphere.

Here are four schemata of this sort.

A. PARIETAL SYNDROMES ASSOCIATED WITH LESIONS OF EITHER HEMISPHERE: (1) Cortical sensory loss; (2) Tactile inattention; (3) Hemianæsthesia; (4) Pseudo-thalamic syndrome; (5) Hemiatrophy; (6) Pseudo-cerebellar ataxia (Gerebtzoff); (7) Constructional apraxia; (8) Visual inattention; (9) Unilateral visual disorientation.

B. PARIETAL SYNDROMES SPECIFICALLY ASSOCIATED WITH LESIONS OF THE DOMINANT HEMISPHERE: (1) Bilateral ideokinetic apraxia (Liepmann); (2) Dyslexic types of aphasia; (3) Pain asymboly (Stengel and Schilder); (4) Anæstho-agnosia (Foix); (5) Spontaneous turning around a vertical axis (Schilder and Hoff); (6) Schilder's syndrome (motor aphasia, apraxia, universal hypalgesia, pathological laughter); (7) Gerstmann's syndrome; (8) visual autotopagnosia (Pick).

C. PARIETAL SYNDROMES SPECIFICALLY ASSOCIATED WITH LESIONS OF THE SUBORDINATE HEMISPHERE: (1) Anosognosia; (2) Imperception of left half of body-scheme; (3) Agnosia for the left half of extra-personal space (Brain) (may be associated with mirror-movements—Hoff and Pötzl).

D. PARIETAL SYNDROMES SPECIFICALLY ASSOCIATED WITH BILATERAL LESIONS: (1) Visual disorientation; (2) Constructional apraxia; (3) planotopokinesia (Marie, Bouttier and Bailey).

All these schemata appear tidy and superficially impressive, but systematization is a dangerous activity, and it does not accord very well with the way we are thinking nowadays about brain activity. It is too reminiscent of the mechanistic conceptions of Bastian, Ferrier, Henschen, Kleist, the Vogts, and so many other materialistic localizationists, whose ideas have sprung from a marriage of the researches of Flourens with an outmoded Cartesian philosophy. Rather than to try and pin-point clinical signs with focal disease, or to construct a sort of cortical mosaic, it would be better to draw attention to certain clinical generalizations which when present are suggestive of parietal lesions, though they are by no means pathognomonic of them.

Among these I would rank as important:

(1) A relative unilateral neglect, without necessarily any gross motor, sensory, or visual disorder. This neglect is shown by a reluctance to use the affected limb even though its motor power is considerable, and even though apraxia, sensory ataxia, and other such handicaps can be ruled out. This symptom of neglect ties up with the importance which parietal integrity plays in the body-image. Within this great category of unilateral neglect belong the phenomena of visual inattention of Poppelreuter, Holmes and others: the tactile inattention of Oppenheim—miscalled "extinction" by Bender and "suppression" by Reider; here also belong certain psychosensory phenomena—usually temporary in appearance and more often seen perhaps with lesions of the minor hemisphere—as, for

example, anosognosia or unawareness of disease; delusion as to the absence of disease; anosodiaphoria or lack of concern over the presence of disease; organic paranoid reaction, or confabulatory explanation of the affected limb, including the so-called "personification anosognosia" of Juba; phantom third limbs; autotopagnosia; the partial autotopagnosia of Gerstmann's syndrome, and of that modification of Gerstmann's syndrome described by von Angyál.

(2) Secondly I would mention the frequency of disorders in the memory of, or in the conception of, spatial relationships, two-dimensional and, more especially, three-dimensional. This defect was first indicated by Quesnel, and is now dignified by Spearman and by Koussy with the symbol "K"—a group factor which is thought to concern the ability to obtain, manipulate and utilize spatial imagery. No doubt Mr. Zangwill will be dealing in greater detail with this important side of parietal disorders. As an elaboration of (1) and (2) we may sometimes witness an additional sequel, namely an unawareness of, or neglect of, one-half of extrapersonal space—so well described by our President—a defect which cannot entirely be ascribed to the mere existence of an homonymous hemianopia.

(3) Thirdly, subtle defects in the highest level of sensory integration. Among these I would like to mention just two, which link up with my earlier remarks, namely (i) tactile inattention and (ii) defective localization of sensory stimuli—a defect which attains its most impressive state in tactile, auditory or visual alloæsthesia (or—more accurately—allachæsthesia), that is, the illusory projection or displacement towards a mirror-opposite point in space.

(4) Fourthly, and arising partly out of these spatial embarrassments, we can refer to particular difficulties in two-dimensional and three-dimensional motor performances—performances which ordinarily are straightforward if not indeed quasi-automatic. I refer of course to the constructional apraxia of Poppelreuter, Kleist, Mayer-Gross, Stengel, and others; the dressing apraxia of Marie, Bouttier and Bailey; Lhermitte; Garcin; also described by our President, but incidentally first noticed by Hughlings Jackson; and even to some of the ideatory and ideomotor forms of apraxia of Liepmann.

(5) Fifthly we have certain handicaps in the domain of language (I use this term advisedly, rather than "speech")—of language and of that aspect of thought which ranges itself with language and which can be called "thinking-in-words". These difficulties naturally involve more heavily the receptive than the expressive side of symbolic formulation. But "motor" defects of language may be at times demonstrated in the so-called "parietal agraphia" of Lange, which forms part of course of the Gerstmann syndrome.

These foregoing sets of defects, what we may call the formulæ of parietal dysfunction, lend themselves readily to a number of quick and easy bedside tests. Of these we can mention the use of Kohs' blocks; simultaneous double stimulation, tactile, auditory and visual; or various drawing tests whereby the patient depicts certain set-themes, e.g. a bicycle (Paterson and Zangwill); a daisy (so revealing of neglect of one-half of space); a map of England (also very striking but unfortunately not yet properly validated as a test-procedure); clock-faces; plans of familiar streets and buildings (Figs. 1—4).

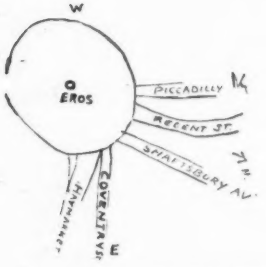


FIG. 1.—Plan of Piccadilly Circus showing relative neglect of left-hand landmarks. Right parietal lesion. (Case No. 182870.)

FIG. 2.—Drawing of a daisy head executed by a patient with a right parietal lesion, showing neglect of detail on the left. (Case No. 22775.)

FIG. 4.—Drawing of a bicycle executed by a patient with biparietal lesions. (Case No. 24033.)

Why do I seem to be critical or, shall we say, feebly enthusiastic over some of these tests of parietal function?

Because in the first place they tell us more about the activities of the relatively intact parts of the brain, and give us a less precise account of where the cerebral defect is situated. When a brain-injured patient draws a grotesque bicycle, we cannot conclude that this is necessarily a parietal deficiency sign, but only that an individual who has cerebral lesion is at that particular moment producing such and such a response to a certain ordained and unfamiliar task.

If we are honest with ourselves we must admit first that many of our patients with parietal disease do not show these alleged parietal signs (these are the so-called "negative cases" of von Monakow); and secondly, that many of these parietal hallmarks are at times produced by lesions remote from the parietal lobe. That useful surgical experiment of leucotomy, for instance, can be followed by a clinical state in which many of these so-called parietal signs can be demonstrated. Visual inattention may be demonstrable at times with frontal lobe lesions. Tactile inattention may even be found with high spinal affections (Brown-Séquard syndromes); spatial disorientation may be seen in cases of frontal tumour; unilateral muscular atrophy (so typical of parietal lesions) may follow temporal disease; and so on.

But one most striking clinical feature of the patient with a parietal lesion is the variability of his performance. He may make a gross error one moment, and give a successful response the next. This makes it important to study closely and to record faithfully just what the patient does during the process of clinical testing. We must not gloss over inconsistencies, or record what we imagine the patient should have done or said. These very irregularities, variabilities, repetitions, hesitancies, changes of mind, erasions, and so on, are, I submit, important. As Holmes and Head noted in their sensory testing of parietal patients, answers may be quite correct one moment, and quite erroneous the next, and later still correct once again. A patient may show time after time well-marked tactile inattention on double stimulation. And then suddenly he may proclaim: "I feel the pin-prick both sides." This is what I have called "extinction of tactile extinction" borrowing Bender's terminology. Again, I regard this sort of phenomenon as characteristic. Or a patient may exhibit tactile inattention at one time on the side opposite to the parietal lesion but a moment later over the other, i.e. the ipsilateral half of the body.

Gnostic defects may show the same paradoxes and vagaries in all spheres. A patient may recognize an apple placed in his hand, but maybe only after a delay—and perhaps only if an apple is placed in the other hand as well. Conversely the patient may recognize an apple placed in his affected hand alone, but not if one is also placed in the unaffected hand. This phenomenon is commoner. Or he may recognize an apple in the hand, but perhaps not some other object placed there a moment later—an orange, or a coin, or a pair of scissors; or he may fail to recognize two objects together in the one hand, though he succeeds with both objects separately. With more posteriorly sited lesions we find similar defects in visual recognition. One object may be identified but only after a delay. Or he may recognize one object but not the next one. Or he may recognize one object but not

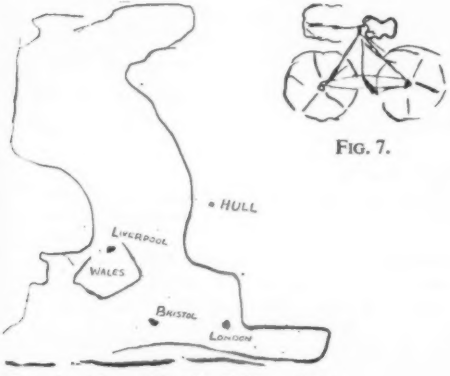


FIG. 3.—Map of England drawn by a patient with a right parietal lesion. Note the shift of topographical detail towards the right. (Case No. 7812.)

FIG. 7.

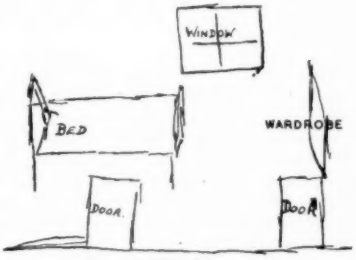


FIG. 8.

FIGS. 7 and 8.—Drawings by patient with a right total hemispherectomy. (Case No. 22684.)

two, whether displayed in opposite fields, or even in the same field; or he may recognize a part of an object (and an intricate part at that) but not the whole. Within the domain of language we may also find variabilities of performance, unpredictabilities, a slowness of execution. with perhaps a perfect end-result, but with imperfect means of achievement.

We can identify in these paradoxes and incongruities a number of fundamental disturbances, such as, for example, fluctuation of attention, ideational inertia, perseveration in the evocation of an easy task to the exclusion of one which is more difficult; lack of demarcation between figure and background; loss of simultaneous function or an inability to cope simultaneously with two tasks, concepts, or percepts; lack of inhibition of associated ideas; the use of cerebral by-passes. All these are phenomena which have been thoroughly described and studied by the Gestaltists, and by the organismic school of neurologists—Lange, Hughlings Jackson, Pick, Head, and Goldstein, who have based themselves upon the philosophies of Herbert Spencer and of Bergson.

Such phenomena are stumbling-blocks in the pathway of those who would nail their tattered banners to the masthead of a rigid cerebral localization. They are additional arguments against the existence within the brain of a hard and fast localization of function—as opposed to a certain specialization of function.

The following are two illustrative contrasting cases:

The first case is that of a man of 64 with a few weeks' history of left hemianopia, clumsiness with the left hand, attacks of myoclonic jerking of the left side, a dressing disability, ignoral of the left side of the body, a grasp reflex in the right hand, spatial disorientation (losing himself in the house), difficulty with writing and later with reading.

Examination showed apraxia and neglect of the left hand; left tactile agnosia and tactile inattention; left hemianopia—visual, auditory and tactile alloæsthesia from left to right; and a left Babinski.

Post-mortem examination showed virtually nothing except a trace of atrophy of the right parietal lobe (Figs. 5, 6).

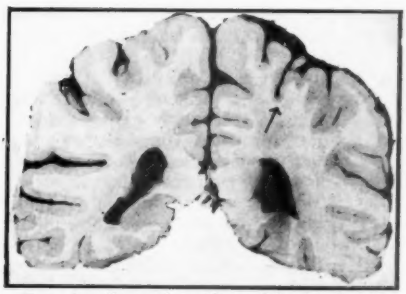


FIG. 5.—Coronal section of brain showing slight degree of cortical atrophy in the depths of a parietal sulcus on the right side. (Case No. 24949.)

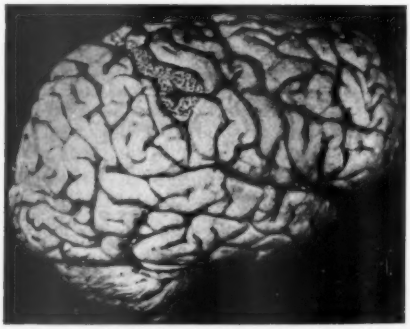


FIG. 6.—Right hemisphere. The dotted area indicates the only region where cortical atrophy could be demonstrated. (Case No. 24949.)

By way of contrast is the case of a girl of 20 years with a left hemiparesis, hemianopia, and hemihypæsthesia. But there was no evidence of specific parietal signs. There was no tactile inattention, no left-right disorientation; no apraxia; no finger agnosia; no spatial defect; and no ignoral of the left side.

Her drawings of her room and of a bicycle are shown in Figs. 7 and 8.

And yet this patient had no parietal lobe at all—nor indeed any right hemisphere. She was the case shown by Mr. L. S. Walsh at last month's clinical meeting, of a total hemispherectomy. (*see* p. 335).

In the one we see a patient with every possible parietal sign—and little or no pathology. That is, no naked-eye pathology but merely minor microscopic changes. The second patient had virtually no specific parietal signs, and yet she had no parietal lobe at all on her right side.

Lastly I would like to register a protest against the claims of the parietal lobe as an anatomical entity. Strictly speaking there is no such structure as a parietal lobe; for it is only an anatomical convention; an empirical demarcation which has been pegged out on the surface of the brain. No natural boundary can be said to exist either behind or below. The traditional gyri and sulci are unhelpful landmarks and are often a matter of guesswork.

To speak nowadays of cortical cyto-architectonic areas is to assume a cloak of precision which is largely threadbare. I grant that a histologist peering down a microscope at a section of cortex can perhaps identify it as belonging to what we call the parietal area but I doubt whether any histologist could tell us whether he is examining the parietal region of the left hemisphere or of the right, even though we are told that the functional significance between them is so very great. I doubt whether he could even distinguish the angular gyrus from the supramarginal.

We know that Betz cells may be detected lying well behind the fissure of Rolando, and also that sensory experiences may result from electrical stimulation far in front of this same fissure. All these are arguments against the conception of the parietal lobe as an autonomous area, either anatomically or physiologically speaking.

What we really need is a new terminology to replace the use of the words "parietal", "temporal", "occipital", and "frontal". I do not quite know what to suggest. There is something to be said for a nautical analogy and for speaking of that region of the cortex in front of the central sulcus, which runs in a vertical direction athwartships, as the "forebrain", and all that which lies behind the sulcus as the "afterbrain". This at least would obviate the strain of any artificial attempts at distinguishing post-parietal from anterior occipital and superior temporal regions of the hemisphere.

Let us remember this historical point, namely that a century ago the brain was not regarded as made up of lobes at all. A little later there was a tendency to speak of anterior, middle and posterior lobes, according to the associated cranial fossæ. Still later someone suggested that that cortical area underlying the *os bregmatis*, or *os parietalis*, might conveniently be called the "parietal lobe". The term eventually caught on, and so it comes about that we find ourselves in the rather artificial position of discussing parietal symptomatology.

Dr. W. Ritchie Russell (Department of Neurology, Radcliffe Infirmary, Oxford): It is, I think, at the age of about 6 months that the human child begins to show the first signs of correlating his sensorimotor system with his visually appreciated environment. If at this age an object is presented in one visual field, the head and eyes begin to make ataxic efforts to turn towards the object, while for the first time the hand next the object is chosen to reach for it. This is almost the first step towards building up the correlation of eye and hand which continues to develop throughout life. This acquired skill consists of three obvious parts. First the child must gradually learn to localize an object in any part of the visual field, in such a way that he can turn his eyes directly to it; secondly, he must learn to localize the parts of his own limbs accurately in relation to his body; and thirdly, he must learn to correlate these two factors to enable him to reach accurately for the object seen. As this faculty also develops quickly in animals we can hardly claim that it represents a very high form of cerebral activity. However, owing to man's superior intelligence, we may perhaps be able to analyse some aspects of these relatively primitive functions. Indeed, a feature of the sensory functions whose correlation we are considering is that they can be analysed to some extent at a conscious level.

However brilliantly the individual may develop his sensorimotor-visual skill there is no doubt that a lesion in one parietal lobe can destroy this faculty as far as both the opposite limbs and the opposite visual field are concerned. As this mechanism depends on sensori-visual correlation it is not surprising that the lesions which destroy it are found to lie between the great sensory and visual projection areas, through which most sensori-visual association pathways must flow.

Many of the wounds caused by fragmentation of high explosive missiles produce small cerebral lesions which provide excellent material for the study of focal brain damage. These wounds may be studied both from the point of view of the symptoms they cause and the symptoms they do not cause. I have charge of the notes of about 300 cases of parietal lobe wounds, many of which have been written by members of this Section. Dr. Michael Kremer examined an instructive case in June 1944.

G. H. (MRC 28), aged 22, was wounded on 23.6.44. There was no loss of consciousness, but the wound caused an immediate paralysis and analgesia (later hyperpathia) of the right arm and face and slight aphasia. The wound caused a small depressed fracture with a very localized area of brain damage visible at operation (Captain P. M. Hartley). The site of wounding is shown in Fig. 1 (K). All the abnormal signs quickly disappeared but during recovery Dr. M. Kremer demonstrated that while there were full visual fields, there was right attention hemianopia and disorientation in right homonymous fields (inability to localize objects). Further he made the important observation that these defects recovered at different intervals after wounding—the disorientation eight days and the attention defect eleven days after wounding.

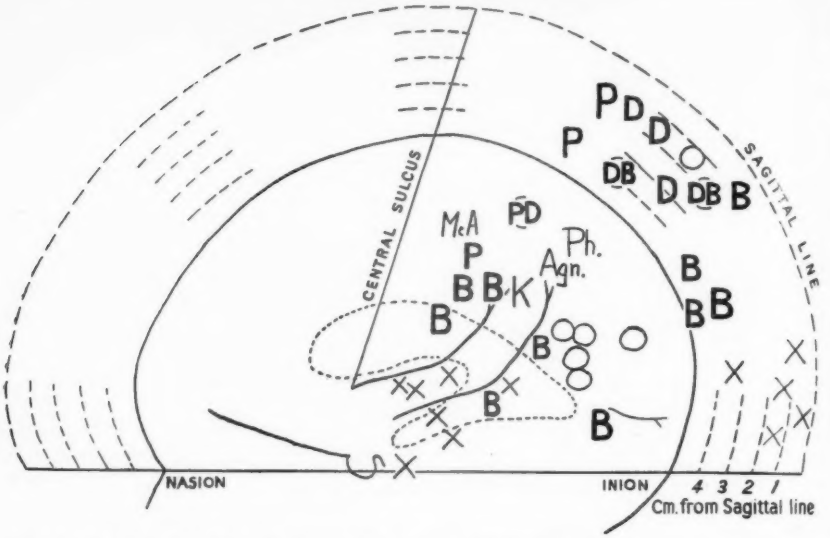


FIG. 1.—Chart to show the site of wounding in certain cases. Charting depends on measurement taken from skull X-rays (Russell, W. R., *Brain*, 1947, 70, 225). Wounds which lie within 5 cm. of the mid-line are placed in the halo outside of the skull outline. P, Cases showing postural loss in one limb only. D, Cases showing visual disorientation in homonymous half-fields. B, Cases showing blurring of vision in homonymous half-fields. X, Cases with pure lesions of optic radiation—steep-edged defects. Ph, Case with epileptic aura of phantom limb. Agn, Case with epileptic aura of agnosia in one limb. O, Cases with no abnormality detected. K, Dr. Kremer's case. McA, Dr. McArdle's case.

Dr. M. J. McArdle also made some careful observations on the disappearance of attention hemianopia after a focal wound.

W. J. H. (MRC 24) was wounded on 26.6.44. There was no loss of consciousness but an immediate paralysis and analgesia of the left arm and face. The wound in the brain seemed to be less than 3 cm. in depth, and its site is given in Fig. 1 (McA). Soon after wounding, Dr. McArdle found full fields of vision but attention hemianopia to left ("splitting the macula"). He watched this defect carefully and found that it cleared up in nine days.

These were temporary lesions of great interest, but cases with permanent disability probably provide more important anatomical evidence, and in considering these we may first refer to lesions which disturb first the appreciation of position of contralateral limbs, and secondly to lesions which disturb the appreciation of position in homonymous half-fields.

LOSS OF POSITIONAL SENSE (UNILATERAL)

Wounds which caused permanent loss of *position sense* in one limb without loss of 2-point discrimination, lie posterior to the post-central gyrus. Four such cases are charted in Fig. 1 (P). Here we are closely concerned with bodily knowledge vital for what we refer to as body image, and in the acute stage after wounding these cases often have temporary agnosia for the limb.

Small parietal lobe wounds causing focal fits can also contribute to the body image story. For example, in Case 86 (Fig. 1 (Agn)), which had a shallow wound near the supramarginal gyrus, there were subsequently some fits which were preceded by an aura in which the patient felt he had lost his right arm.

Again in Case 71 with a small wound, in much the same place (Ph), the aura sometimes consisted of the sensation of a phantom arm above the patient's head when his arm was in fact at his side—this patient, however, also had fits in which the arm did actually rise above his head.

Disorientation in Half-fields

Most cases of disorientation or inattention in homonymous half-fields appear in cases of hemiplegia in which the lesion extends backward from the sensorimotor region into the parietal lobe.

However, in this series of cases there is no difficulty in finding some with isolated inability to localize objects seen in half-fields, without sensorimotor disorder, and it seems clear that the wounds which cause this disability are deep (often 4–6 cm.) and penetrate the parietal lobe not far from the sagittal sinus. The position (D) of entry of six such wounds is shown in Fig. 1. The wound tracks were generally vertical, narrow and deep (over 4 cm.).

In these cases the disability is permanent and it is interesting to note that these wounds lie immediately posterior to that part of the brain where lesions cause loss of position sense in the opposite limbs. The considerable depth of these wounds suggests that this disability is probably not due to destruction of an area of cortex, but to division of association pathways, possibly those connecting the sensory cortex and the higher visual peristriate area.

Lack of Attention and Extinction in Homonymous Half-fields, &c.

There are two other visual phenomena I should like to consider further. The first concerns the common "attention hemianopia" in which a simultaneous movement in the seeing field makes it impossible to see a movement in the affected field. This also occurs with the somatic sensory functions, and is not really a lack of attention but a striking inability to see or feel on the affected side if a simultaneous stimulation is made on the sound side.

Associated sometimes, but by no means always, with this attention hemianopia, is a curious defect in visual acuity in homonymous half-fields, as a result of which small stationary objects disappear in the affected half-field, but immediately reappear if the object is moved or if the subject blinks (Fig. 1, B).

One fact which emerges pretty clearly from the records available is that these defects of distinctness are not due to partial lesions of the optic radiations, for the latter when pure seem to produce sharp-edged defects. It seems likely that partial or shading defects of homonymous fields are due to peri-calcarine lesions, and are clearly a higher level of disorder than is caused by a lesion of the radiation alone (Fig. 1, X).

I would suggest two explanations of these abnormalities. The blurring and loss of a stationary object may well reflect the effect of a peristriate lesion. As with most other areas of the cerebral cortex, it is unlikely that the peristriate areas of cortex will act properly without their thalamic (pulvinar) connexions and these may be divided by deep parietal lobe lesions as well as by direct involvement of the posterior peristriate cortex, as is suggested by the varying site of lesions (Fig. 1, B).

The second suggestion concerns the phenomena of inattention for, or extinction of, a sensory or visual stimulus when the normal side is stimulated. These disorders are permanent only in severe and deep lesions of the parietal lobe. It seems to me that the most likely anatomical explanation is that the damaged hemisphere is so disabled that the other (homolateral) hemisphere is of necessity being used by relay. This involves delay and a stimulus arriving normally from the contralateral side is sufficient to block the later and circuitously arriving projection from the homolateral side. I would suggest therefore that the "attention defect" phenomena depend simply on competition from both sides of body and visual field to use the one undamaged hemisphere.

Mr. O. L. Zangwill (Institute of Experimental Psychology, Oxford): In a recent review of cortical localization, Sir Geoffrey Jefferson (1950) has drawn attention to the important linkage between spatial orientation and the parietal cortex of both hemispheres. This correlation, which first became apparent through Holmes's classical studies of visual disorientation (1918, 1919), has attracted much interest in recent years (cf. Riddoch, 1935; Russell Brain, 1941; Critchley, 1949; Purdon Martin, 1949). Approaching the subject as a psychologist, I have been concerned for some years with the finer analysis of visual-spatial disabilities. Although this work is still in progress, and few general conclusions can be drawn, I am hopeful that some of our findings will not prove without relevance to this discussion.

We are at present undertaking a survey of cases of posterior penetrating brain wounds in the records of the Head Injuries Bureau at Oxford. This work has been made possible by the generous encouragement of Dr. Ritchie Russell and by the excellence of so many of the original investigations and case reports. Much of the preliminary classification of the

material has been undertaken by my colleague Mr. M. E. Humphrey, of the Oxford University Institute of Experimental Psychology. Up to the present, we have worked through the records of 110 cases of parietal, parieto-occipital and occipital injuries, of which 26 are recorded as having shown defects of spatial orientation at some stage after injury. 8 have so far been followed up and studied in detail. Although we hope eventually to present a full analysis of the findings in all cases with spatial defect, together with evidence bearing upon its localization, most of this report is based upon the 8 cases which we have studied personally.

The 8 patients in the present group were all of at least average intelligence and educational standing. 3 were former officers, of whom 2 possessed University degrees. The lesion was left-sided in 3 cases and right-sided in 5. In 3, however, some degree of bilateral involvement was suspected. The locus of the lesion could be broadly described as posterior parietal in all cases. Residual dysphasic signs were present in 4 cases but pronounced in only 1. All patients were right-handed but the presence of dysphasia in 1 patient with a right-sided lesion suggested some anomaly of cerebral dominance in his case. 6 patients presented permanent visual field defects: in 3 a left and in 1 a right homonymous hemianopia; in 2, lower quadrantic defects. All 6 appeared to have adjusted satisfactorily to their field defects but in 2 there was evidence of some tendency to neglect the left half of visual space (Russell Brain, 1941). Apart from field defects, residual neurological signs were minimal or absent.

All patients were aged between 20 and 30 at the time of injury and, with one exception, were interviewed by Mr. Humphrey and myself about five years after discharge from hospital. The exception was a man of 56 who sustained a right occipito-parietal shrapnel wound in the 1914–18 war and who was referred to us on account of a thirty years' history of topographical disorientation. The remaining 7 patients had been examined by the late Major W. R. Reynell at an early stage after injury and his reports show that all had sustained a circumscribed intellectual loss on visual-constructive tests and on a variety of tasks presumed to involve visualization. In only 2 cases, however—both complicated by dysphasia—was there evidence of more widespread intellectual deterioration. Personality changes were minimal throughout.

The principal defects bearing on spatial orientation.—More limited spatial defects, such as disorientation in homonymous half-fields, have been excluded from consideration owing to their somewhat specialized nature. Broadly speaking, the defects with which we are concerned fall into three groups. First, minor grades of visual disorientation (visual-spatial agnosia); second, loss of bearings in familiar surroundings; and third, more severe grades of topographical loss. Although these varieties of defect show considerable overlap, it is perhaps permissible to treat them separately for purposes of discussion.

Minor grades of *visual disorientation* were shown by 4 patients, in all of whom the lesion was right-sided. In 1, the defect amounted to a mild degree of true disorientation in central vision. This patient made slight, though definite, errors in relative distance judgment and had probably sustained some impairment of depth perception. He complained that his visual world was "rather flat—not the same as most people's". In the other 3 cases, defects were elicited only when fine estimations were demanded. Although well brought out by the types of test I have described elsewhere (Paterson and Zangwill, 1944), they are perhaps even better illustrated by the patient's own testimony. Thus one officer told us that when attending a rehabilitation course he had been unable to place a vaulting horse at right-angles to his line of run-up. He could appreciate the misalignments but was powerless to correct them. Five years later, he related that he still had difficulty in correctly replacing articles of furniture which had been accidentally shifted. Another patient, by profession an actor, reported such severe difficulty in finding what he called "the right place on the stage" that he had been obliged to seek a less exacting occupation. A third patient, employed as a gardener, found himself unable to plant seeds in regular rows and was always obliged to seek assistance in this aspect of his work. Although defects of this character do not necessarily entail loss of topographical sense, they can interfere appreciably with finer spatial adjustments. Further, although the locus of the responsible lesion cannot yet be defined with complete precision, such defects appear to bear a rather special relation to the parietal lobe of the minor hemisphere. This finding, though contrary to conventional opinion, finds some support from a number of recent studies (cf. McFie, Piercy and Zangwill, 1950).

Brief episodes of *spatial disorientation* were reported by 6 patients. They took the form of *transitory loss of bearings in familiar surroundings*, rendering the patient liable to proceed in the wrong direction or even to become momentarily lost. In 2 cases, at least, it was probable that the disturbance involved the body scheme as well as visual space perception. Thus one case of left-sided occipito-parietal injury, on interview three and a

half years after discharge, reported that he was apt to lack an "immediate sense" of his whereabouts. This rendered him likely to enter the wrong room, even in his own house. On one occasion he bent down to tie his shoe-lace, and, on standing up, believed himself to be facing the other way and took several steps in the wrong direction. In this, and one other case, uncertainties regarding right and left might likewise lead to momentary loss of bearings. It is not without interest that spatial defects of much the same character were described by Marie and Behague (1919) in certain cases with deep unilateral injury of the frontal lobes and their subjacent connexions. These findings lead one to surmise that loss of topographical sense is not invariably based on visual-spatial agnosia. As Claparède (1943) has suggested, it may have an important relation to the higher forms of body apraxia associated with lesions of the major hemisphere.

The wider aspects of topographical loss.—All patients in this group reported *difficulty in learning their way about* in unfamiliar surroundings, and in 5 this remained a severe residual handicap. One patient was very loath to visit new places on account of his slow and insecure topographical learning. Another told us that it took him a matter of weeks to learn his way around a market-garden in which he was at one time employed. A third confessed to similar difficulty with regard to a large office building in which he had worked for a considerable time. This defect may be due, in part at least, to a more general impairment of visual retention. At all events, it was noteworthy that several of these patients complained also of slowness in learning to recognize new faces and of some impairment of visual imagery. Such defects, however, have occasionally been reported in the absence of topographical loss.

In the second place, at least 5 patients in this group gave evidence of a form of disorientation which appeared to be due to a defect of *topographical memory*. It was found to vary in severity from mere diminution of the sense of familiarity in long-known surroundings to gross failures of recognition and route-finding. One patient, indeed, had been unable for thirty years to proceed through his native city without an escort. It was noteworthy, further, that the degree of topographical loss showed some relationship to the familiarity of the setting. Thus one patient, a Londoner, could always find his way about in the vicinity of his own home but was apt to get lost in other parts of London previously well known to him. A second patient stated that he could find his way about much more readily in the city in which he had been brought up than in the town in which he had spent three years as a University student. It is probable, therefore, that topographical memory loss obeys what used to be called the law of regression (Ribot, 1885).

We have attempted to make some analysis of the factors responsible for loss of topographical orientation. This syndrome appears rather complex and the underlying deficits may vary considerably from case to case. In 2 of our cases, for instance, errors in route-finding were undoubtedly due in part to neglect of the left half of space with a consequent preference for right-hand turns in the manner described by Russell Brain (1941). In 3 cases, spontaneous reference was made to loss of the quality of familiarity in habitual surroundings. For example, one patient told us that when walking in places well known to him he often felt that he did not know what was round the next corner and that the scenery unfolded as though he were in a strange country (cf. Spalding and Zangwill, 1950). He might or might not become lost under these circumstances. In general, we appear to be dealing with a high-grade defect of recognition which impairs topographical sense without necessarily abolishing it. As Critchley (1949) has pointed out, phenomena of this kind associated with parietal lesions are reminiscent of derealization, with which they may well be ultimately related.

Somewhat similar restrictions of topographical memory were noted in several patients whose orientation in practice was as a rule intact. These patients commonly had great difficulty in indicating the directions of neighbouring buildings whose names they knew or in giving directions as to routes which, in practice, they could follow adequately. Compass directions were apt to give especial difficulty. Such defects are clearly reminiscent of the spatial difficulties described by Head (1926) in his cases of semantic aphasia. In our material, however, aphasia did not appear to be a necessary condition for their appearance. In yet other cases, a certain restriction of synthetic grasp of the wider spatial setting was apparent. As one of our most intelligent patients put it: "It is not recognizing buildings that gives me trouble but mastering the general lay-out." In these cases, there is a curious fragmentation of the visual world. The patient is able to recognize rooms and buildings but he cannot relate them to a coherent topographical scheme. Whether this disorder is, at bottom, one of perception or of memory is hard to determine. Perhaps we might evade the difficulty by referring to it as *topographical agnosia.*

Certain *compensatory reactions to topographical loss* were observed in our follow-up studies. Several patients were found to have built up simplified verbal schemes to assist them in route-finding and in the recall of topography. One man, who knew Oxford well, always oriented himself in this city by reference to the clock-tower at Carfax. He had worked out serial lists of landmarks, based on Carfax, by means of which he identified his main routes. If an expected landmark failed to materialize, he would retrace his steps to Carfax and start afresh. On one occasion we accompanied him on his way through Oxford and verified the procedure. In other cases, small details presented by rooms and buildings were used for purposes of identification (cf. Paterson and Zangwill, 1945). These points might prove relevant to the re-education of patients with topographical disabilities.

In summary, our work has led us to distinguish three groups of higher spatial defect associated with parieto-occipital lesions of the cortex. First, minor grades of visual disorientation, especially prominent in cases with lesions of the minor hemisphere. Second, disorders in appreciating position and direction with regard to one's own body, probably related to the higher forms of body apraxia and thus to lesions of the major hemisphere. Third, disturbances of place-recognition and route-finding which in many cases presuppose some loss of topographical memory. Although conventionally ascribed to the major hemisphere, topographical memory (on present evidence at least) does not appear to be narrowly subject to the principle of cerebral dominance.

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